VOLUME 29 NUMBER 1

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Archives of Internal Medicine

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MOTOR PHENOMENA OCCURRING IN NORMAL STOMACHS, IN THE PRESENCE OF PEPTIC ULCER AND ITS PAIN, AS OBSERVED FLUOROSCOPICALLY *

LAWRENCE REYNOLDS, M.D., AND C. W. McCLURE, M.D.

BOSTON

This communication embodies the principal results of fluoroscopic observations of the stomachs of normal men and of patients with ulcer of the stomach or duodenum, after the feeding a meal composed of meat and barium, which we have recently made. The ulcer patients were studied in order to obtain detailed information regarding gastric motor phenomena occurring throughout the period in which the stomach was emptying itself and during the occurrence of pain due to the presence of the ulcer; and, also, to attempt to establish an objective method for determining the effects of therapeutic measures. The normal patients were studied to obtain further data as to normal motor activity. It may seem that there is no need for further roentgen-ray observations on the motor activities of the normal human stomach, for considerable data [1] are available describing such observations after the ingestion of various kinds of solid foods. But clinicians and physiologists do not always seem to be cognizant of this fact as judged from statements found in current textbooks of medicine. For example, a recent leading system of medicine contains the statement, "then by means of onward circular constriction the material is pressed toward the pylorus, but the pylorus opens only at intervals and not with every peristaltic wave. In fact, many peristaltic waves will frequently be seen before the pylorus relaxes." [2] While this statement holds true, accepting Cannon's [3] observations, for the stomach of the cat the work of Cole [4] and ourselves,[5] among others, shows that in normal man the pyloric sphincter

* From the Radiographic Department and the Medical Clinic of the Peter Bent Brigham Hospital.

1. Carman, R. D., and Miller, A.: The Roentgen Diagnosis of Diseases of the Alimentary Canal, Philadelphia and London, 1920, p. 110.
2. Rehfuss, M. E.: Oxford Medicine, New York **3**:29, 1921.
3. Cannon, W. B.: Am. J. Physiol. **1**:359, 1898.
4. Cole, L. G.: J. A. M. A. **61**:762 (March 6) 1913; Am. J. Physiol. **43**: 618, 1917.
5. McClure, C. W.; Reynolds, L., and Schwartz, C. W.: Arch. Int. Med. **26**:410 (Oct.) 1920.

relaxes as each and every peristaltic wave approaches that orifice. This observation, alone, indicates the advisability of making more studies on the stomach of normal man.

For the purposes of the present investigation all subjects were fed one type of meal. The meal consisted of 160 gm. of finely ground, lean beef and 40 gm. barium sulphate baked in a loaf. Before feeding it, the loaf was ground up with sufficient water to make a thick mush, or was given in its dry state along with from 150 to 200 c. c. of water to drink, while to one subject it was given in the dry state without water to drink. The stomachs of the subjects were observed fluoroscopically immediately after the period of ingestion, a few minutes, then at fifteen minute intervals for one hour, and then at thirty minute intervals for two hours and then at hourly intervals until the stomach was nearly empty, when observations were made at more frequent intervals. Five normal subjects and sixteen patients with peptic ulcer were studied.

Immediately after the meal had been ingested by the subjects the stomach was seen to be about three-fourths filled, if observations were made with the patient in the erect posture. The air bubble in the fundus occupied the remaining fourth of the gastric cavity. As the stomach emptied, the upper level of the food gradually became lower until only the outline of the pyloric region was visible. While this was occurring that part of the outline of the stomach which was still visible was not modified appreciably in shape until but a small residue remained, which latter formed a hemispherical outline along the greater curvature just proximal to the pyloric sphincter. At this time, if the patient was standing, the sphincter was seen to occupy a position above the residue, the latter would roll back over advancing peristaltic waves and consequently would not be ejected through the sphincter into the duodenum. However, in the reclining position the residue lay up against the sphincter and each peristaltic wave forced a portion of it over into the duodenum, except when pylorospasm was present.

In the stomachs of the five normal subjects as soon as the pyloric region contained food, peristaltic waves were observed to eject barium containing chyme through the sphincter into the duodenum, as each wave approached that orifice, except in one subject. In the latter, gastric peristaltic waves were very shallow during the first twenty-five minutes after the meal was ingested, and no barium was seen to enter the duodenum; peristalsis then became active and the remaining phenomena corresponded to that seen in the other subjects. Peristaltic waves began as shallow indentations at about the junction of the upper and middle thirds of the stomach's outline and progressively deepened to about the midpyloric region, where the waves approximately half way bisected the stomach, while in the immediate neighborhood of the pyloric

sphincter the gastric outline was either almost or completely bisected. Waves began at regular intervals, roughly judged to be twenty seconds each, but accurate time measurements were not made. To the eye each peristaltic wave went through the same series of phenomena as it coursed along the stomach from its origin to the pyloric sphincter. The same peristaltic phenomena were observed in the subject who ate the meat and barium loaf in a dry state and without drinking water. In the stomach of this subject, during the first thirty minutes after ingesting the meal, the majority of the latter formed a globular mass below the air bubble in the fundus, while a smaller portion formed a long, narrow neck extending from the lower end of the globular mass to the pyloric sphincter, the whole appearing much like an inverted gourd. The outline of the stomach appeared very irregular due to the dry state of the contained food. Barium began to leave the stomach as soon as the meal was ingested, i. e., a few minutes. Within thirty to forty minutes after the ingestion of the meal this stomach had assumed the shape similar to that observed in the other four subjects and had, also, lost the irregularity of its outline.

Four of the normal subjects occupied the erect position throughout the period of observation. In three of these the stomach contained a small residue at the end of five hours. Peristalsis was active at this time in the stomachs of two of the subjects but was unable to eject barium into the duodenum for the reasons given. In the stomach of the third subject, peristalsis was no longer present. A medium sized residue remained in the stomach of the fourth subject at the end of seven hours. Peristalsis was active in the stomach of this subject for the first five hours after the meal was ingested, but during the sixth and seventh hours of the period of observation it was intermittent and feeble or absent. The stomach of the fifth normal subject, who was reclining throughout the entire period of observation, emptied itself in five hours.

In all the normal subjects the first portion of the duodenum filled out fairly well, but its outline was not as smooth nor its circumference as great as after the liquid meal ordinarily employed for diagnostic studies. Roentgenograms of the stomach and intestines of the normal subjects allowed the meat and barium meal to be followed through the small intestines and into the cecum. In about forty-five minutes the jejunum was seen to contain much barium. The ileum was reached by the barium in an hour to an hour and a half and the cecum in four to five hours. In one of the subjects the head of the barium column had reached the hepatic flexure at the end of five hours.

Gastric motor phenomena, as observed fluoroscopically, in the presence of ulcer in the stomach or duodenum showed in fourteen of the sixteen patients studied, either constantly or intermittently, devia-

tions from those observed in the absence of such a lesion. The abnormal motor phenomena were the same whether the ulcer was located in the stomach or in the duodenum, except that in gastric ulcer peristaltic waves did not course over the area of ulceration; this has been described in a previous communication.[6] Other than this, five types of abnormal gastric motor phenomena were observed, as follows: (1) exaggerated type of normal peristalsis; (2) irregular peristalsis; (3) antiperistalsis; (4) pylorospasm; and (5) the presence of an incisura in the greater curvature.

Exaggerated Type of Normal Peristalsis.—This type of peristalsis was observed in seven patients with ulceration of the first portion of the duodenum. It persisted throughout the emptying periods of the stomachs of four subjects and during a two hour period of observation of a fifth. In the sixth subject the exaggerated type of peristalsis was changed to the irregular type, described below, with the onset of pain, and in the seventh subject this change occurred without the onset of pain.

In the presence of exaggerated peristalsis the number of waves observed at any one time in a given stomach was constant, but the number of waves varied from one to three in the different individual stomachs. By the time a wave had progressed from its point of origin in the fundus to the beginning of the lower third of the stomach it either completely or almost completely bisected the stomach. These deep waves pushed a considerable amount of gastric contents before them, either filling the pyloric region of the stomach abnormally full and giving rise to the so-called "prepyloric bulge," or sending large amounts through the sphincter into the duodenum. Pylorospasm was discernible intermittently in five of these stomachs.

Irregular Peristalsis.—This type of peristalsis occurred in the stomachs of seven of the patients studied. It was characterized by marked variation in the time of appearance, duration and depth of the peristaltic waves. Beginning at the usual site a wave would course along the stomach distances varying from a few centimeters to as far as the plyoric sphincter. An occasional wave, reaching as far as the sphincter, would eject barium into the duodenum; this showed the absence of pylorospasm. More often, either the waves died out before reaching the pylorus or no peristalsis was visible. Under these circumtances the gastric peristalsis was not of such a character as to permit it to eject barium through the sphincter into the duodenum, and for this reason it was not always ascertained whether or not pylorospasm was present. However, certain of the peristaltic waves, which occasionally reached the pyloric sphincter, did not eject barium into the duodenum; at which times pylorospasm was considered to be present.

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6. McClure, C. W., and Reynolds, L.: J. A. M. A. **74**:711 (March 13) 1920.

The irregular type of peristalsis persisted throughout the emptying period of the stomach in one patient and until after the cessation of pain in another. It began with the onset of pain in five patients; prior to the onset of pain peristalsis was of the normal type in three of these patients and of the exaggerated type in two. After the cessation of pain either through natural means or after the administration of sodium bicarbonate, peristalsis became of the normal or nearly normal type and the stomachs emptied rapidly.

Reversed Peristalsis.—In two patients the pyloric sphincter was found to be in a state of spasm during observations made over periods of about three and a half and six hours after the ingestion of the meal. During these periods antiperistaltic waves took origin at the pyloric sphincter and coursed back over the stomach a variable distance.

Pylorospasm.—Pylorospasm is defined as the failure of the pyloric sphincter to open or to open its normal width, as judged fluoroscopically, in relation to the advance of a gastric peristaltic wave; i. e., the sphincter opened partially, as judged by the small amount of barium seen to enter the first portion of the duodenum, or it remained closed, as judged by the failure to see barium enter the duodenum. Prolonged pylorospasm frequently accompanied the exaggerated type of gastric peristalsis, while it was observed in but one stomach in which the peristaltic waves were very shallow. The pylorospasm was usually intermittent.

Incisura.—In one patient a small penetrating ulcer occurred at about the midpoint of the outline of the lesser curvature of the stomach. Opposite the ulcer an incisura, invaginated from the greater curvature side, almost bisected the stomach, thereby dividing the latter into a lower and upper loculus. The patient's predominating symptoms were nausea and vomiting, unaccompanied by pain. She was unable to ingest more than a half of the usual meat meal because of the onset of nausea. On fluoroscopic examination it was found that the portion of the meal eaten completely filled the upper loculus of the stomach, and that very little of the food had entered the lower loculus. In spite of the complete filling of the upper loculus the patient did not experience a sensation of fulness. Within fifteen minutes after the ingestion of the meal eaten completely filled the upper loculus of the stomach, and that incisura was less deep. Active peristalsis was present in the pyloric region at this time and the sphincter was acting in a normal manner. Twenty minutes later the upper loculus of the stomach was found to be empty, and within a total period of three hours the stomach was found empty.

In four patients a small incisura developed in the greater curvature of the stomach coincidently with the onset of pain, which will be discussed later.

Pain.—During the period of observation twelve patients with peptic ulcer complained of epigastric pain. The character of the pain was severe in five, moderately severe in two, mild in two and mere discomfort in three. The pain developed between one hour and two and a half hours after the ingestion of the meal in all but one patient in whom discomfort developed thirty minutes after the meal. The onset of severe or moderately severe pain in four of the patients was preceded by milder pain over periods varying from five to thirty minutes. The onset of all types of pain was accompanied by distinct modifications in whatever type of motor activities the stomach had previously manifested, except in two patients who will be discussed later. If the peristalsis was of the exaggerated type with pylorospasm, the onset of pain was heralded by an increase in the depth of the waves or in the degree or duration of pylorospasm or both, except in one case in which the exaggerated peristalsis became the shallow type. If irregular peristalsis preceded the onset of pain, when the latter developed, the irregularity became more pronounced or peristalsis ceased altogether. If peristalsis had been normal before pain developed, it then ceased or became of the irregular type. In four cases with pain a small but definite incisura developed in the greater curvature, near the upper level of the barium shadow, with the onset of pain. In one of these the incisura accompanied mild pain a half hour before the severer pain occurred. In two of these the incisura was the only demonstrable abnormality developing coincidently with the onset of pain.

After cessation of pain peristalsis became normal, or nearly so, and the stomach rapidly emptied itself, except in two cases in which exaggerated peristalsis with intermittent pylorospasm remained. After the onset of severe pain in one patient and mild pain in two others, 3 gms. sodium bicarbonate or 2 gms. sodium bicarbonate with 1 gm. calcium carbonate suspended in 20 c. c. water were administered. Within from three to ten minutes after taking, the pain disappeared, and simultaneously the abnormal motor phenomena in the pyloric sphincter and stomach, including the incisura in one case, disappeared. In a fourth subject with the onset of moderate pain an incisura developed in the greater curvature of the stomach, while peristalsis and the behavior of the sphincter remained normal. The patient was given 20 c. c. tap water to drink, immediately after which peristaltic waves became deeper while the pain remained the same. Twenty-five minutes later 3 gms. sodium bicarbonate suspended in 20 c. c. tap water were taken. Ten minutes later all pain had ceased but gastric peristalsis remained unaffected and the incisura persisted. Just prior to the disappearance of pain after the administration of alkalis to these four patients it was noticed that the gas bubble in the fundus of the stomach was much increased in size.

Two patients, in whom ulcers were located in the first portion of the duodenum, were observed in whose stomachs no modifications of peristalsis occurred with the onset of pain. The type of peristalsis present in the stomach of one of these patients was the exaggerated type and in the other the waves were perhaps somewhat deeper than normal. Both subjects developed mild epigastric pain lasting fifteen and thirty minutes, respectively.

Four patients in whom active ulcers were located in the first portion of the duodenum were studied in whom no pain or discomfort developed during the period of observation after eating the meal. However, the ulcers present in these patients were of the acutely painful type and pain had been present up to the day of observations here reported. Two of the patients were observed over periods of two and three hours only, during which times the stomachs showed the exaggerated type of peristalsis; pylorospasm was present in one of these and but very little barium entered the intestines. The stomachs of the other two were observed throughout the period of emptying. One showed exaggerated peristalsis without pylorospasm and emptied in three hours and twenty minutes. The other showed a marked type of irregular peristalsis without pylorospasm and emptied in five hours.

Pain developed in eight of the patients at times when the amounts of food present in the stomachs varied from the quantity ingested to half that amount. The development of pain was delayed until the stomachs were nearly empty in four patients.

Emptying Time of the Stomach.—While the normal stomach was not quite empty at the end of five hours, in the presence of peptic ulcer the stomach was, with few exceptions, completely empty in three and one-half to four hours. The emptying time of the stomach of one patient was much delayed in the presence of prolonged pylorospasm. Delayed emptying time was not observed in any other condition. In one stomach in which the irregular type of peristalsis was present, there was an initial delay in emptying. This was evidently the result of the infrequency of peristalsis in the presphincteric region, since, whenever a peristaltic wave reached that region, barium was ejected into the duodenum. Nevertheless, this stomach emptied itself of barium in four hours. In another patient, with an ulcer in the first portion of the duodenum, the stomach emptied itself in three hours. Peristalsis was of the one wave type and during the first half hour after the ingestion of the meal peristaltic waves were regular in time but irregular in depth and almost complete pylorospasm was present. Peristalsis then became regular in the depth of the waves, spasm of the pylorus ceased and during the succeeding two and one-half hours the stomach emptied itself.

SUMMARY AND DISCUSSION

Fluoroscopic observations on the normal human stomach, after the ingestion of finely divided meat mixed with barium, show that it empties itself in a regularly progressive manner. Peristaltic waves begin high up in the gastric walls at uniform intervals of about twenty seconds and gradually deepening progress in an orderly manner to the region of the pyloric sphincter. As each wave approaches the sphincter the latter opens, allowing chyme to be ejected into the duodenum over a period of about ten seconds.[5] With the subject in the reclining position, one of the normal stomachs emptied itself in five hours. Three of the normal stomachs were almost empty in five hours; under the conditions of the observations here reported a very small residue remained along the greater curvature of these stomachs for a longer period. The stomach of the fifth subject contained a moderate sized residue at the end of seven hours.

Abnormal phenomena observed in the stomachs of patients with duodenal or gastric ulcer were modifications of the motor activities of the stomachs of healthy persons. The abnormalities noted were: (1) an exaggerated type of normal gastric peristalsis; (2) irregularity in the time of occurrence, depth and length of the course of peristaltic waves; (3) partial or complete intermittent spasm of the pyloric sphincter; (4) localized, permanent, stationary spasm of the gastric musculature causing the so-called incisura; (5) gastric antiperistalsis; (6) delayed emptying time of the stomach; and (7) very rapid emptying of the stomach. The onset of pain was accompanied by modifications in whatever type of motor activities the stomach had previously manifested, with two exceptions. The various abnormal motor phenomena were observed in the stomachs of peptic ulcer patients who did not develop pain during the period of observation.

The abnormal motor phenomena described are familiar to all clinical roentgenographers. But their relation to the pain of peptic ulcer as observed fluoroscopically has not been previously systematically studied. On the other hand, the relation of gastric motor phenomena to the pain of peptic ulcer has been studied by the well-known balloon method by Carlson,[7] Hardt,[8] Hamburger,[9] Homans,[10] and others. Carlson and Hardt state that the pain of ulcer is the result of contractions of the musculature of the stomach, pylorus (pyloric sphincter) or first portion of the duodenum. Their evidence that pain is accompanied by pyloro-

7. Carlson, A. J.: Am. J. Physiol. **45**:80, 1917.
8. Hardt, L. L. J.: J. A. M. A. **70**:837 (March 23) 1918.
9. Hamburger, W. W.; Tumpowsky, I., and Ginsburg, H.: J. A. M. A. **67**: 990 (Sept. 30) 1916.
10. Homans, J.: Am. J. M. Sc. **157**:74, 1919.

spasm or contraction of the duodenum is entirely indirect and consequently its existence in their experiments is problematical. Furthermore, Homans observed pain at a time when the balloon method failed to show the presence of peristalsis in the stomach. These contradictory findings are explained by our observations, since we found peristalsis might be either active or absent during the presence of pain.

While Carlson frequently did not observe modifications in gastric peristalsis in the patients with peptic ulcer which he studied, we observed them in fourteen of the sixteen patients which we studied. The frequent failure of Carlson to observe modifications of gastric motor phenomena during the presence of pain may be explained in two ways: (1) the balloon method permits recording of gastric peristalsis only, and by it small incisurae or pylorospasm are not ascertainable; and (2) as Luckhardt and Carlson [11] note, peristalsis as observed by the fluoroscope was not accurately recorded by the balloon method.

It has already been noted that we could not always determine the presence or absence of pylorospasm during the time of occurrence of pain. For this reason, and since the balloon method does not directly demonstrate pylorospasm, whether or not spasm of the pylorus always accompanies pain remains undetermined. However, we have made one observation which suggests that pylorospasm may be absent during the occurrence of pain. This observation was made on a subject with an active ulcer in the first portion of the duodenum. On one occasion the patient voluntarily complained of severe epigastric pain at a time when fluoroscopic observation showed barium to be passing through the pyloric sphincter in an apparently normal amount and manner. The next peristaltic wave, however, showed the presence of complete pylorospasm, although the pain had ceased.

The essence of our findings regarding the relation of peptic ulcer pain and motor phenomena of the stomach and pyloric sphincter is that during the presence of pain abnormalities of these motor phenomena are usually demonstrable. But merely because of this the conclusion reached by most observers, that motor phenomena are the cause of the pain of peptic ulcer, is not necessarily correct. Evidently these observers have as a basis for this conclusion the reasoning from the analogy that spasm of voluntary muscle can cause pain. But, on the other hand, spasm of voluntary muscle is also commonly a phenomenon protecting against the development of pain. Therefore, the mere association of the abnormal motor phenomena and pain, which we found in our observations, does not in itself determine the causal relation of the

11. Luckhardt, A. B.; Phillips, H. T., and Carlson, A. J.: Am. J. Physiol. **50**:60, 1919.

two. However, it seems plausible to assume that muscular movements surrounding an ulcerated area in the stomach and duodenum could cause pain, provided pain nerves were present. But such an assumption does not explain why the pain does not usually persist throughout the entire emptying time of the stomach, nor why pain occurs early after food ingestion in some patients and late in others. The fact that pain did not always accompany abnormal gastric motor phenomena or pylorospasm could be explained on the theory that the degree of muscle spasm was not sufficient to produce pain. This theory could also explain the observation that pouring tenth normal hydrochloric acid onto a duodenal ulcer through a duodenal tube produced, without any subjective sensations, pylorospasm, cessation of gastric peristalsis and duodenal antiperistalsis in one patient which we studied. But it is to be emphasized that there is no means to prove such a theory. From this discussion it is evident that the fact that the two phenomena, normal or abnormal gastric or sphincteric motor phenomena and the pain of peptic ulcer, occur simultaneously does not conclusively demonstrate that motor phenomena cause the pain.

Hurst [12] and others have found that distention of the stomach or intestines by blowing them up with air to a sufficient pressure causes pain. Because of this finding Hurst proposed the theory that gastric or intestinal pain was the result of forceful distention of the gut wall due to violent contraction on material in the lumen of the gut of the section of the wall immediately above the distended region. Undoubtedly pain can be caused by the method employed by Hurst, but there is no experimental proof demonstrating that distention of the magnitude produced by it occurs as the result of the presence of peptic ulcer. Furthermore, we have observed, as has Homans, complete cessation of peristalsis in the stomach during the occurrence of pain; since under these circumstances no peristalsis occurred, there could not have been the distention produced as postulated in the theory proposed by Hurst.

This discussion shows that no motor phenomena are peculiar to the occurrence of the pain of peptic ulcer, that there is at present no accurate means available for measuring the degree of spasm of the gastric or sphincteric musculature, and that there is almost no support for the distention theory proposed by Hurst. In view of these facts it is evident that there is no incontrovertible proof that the pain of peptic ulcer is the result of motor disturbances in the stomach and pyloric sphincter. The most satisfactory evidence in support of the theory that such motor disturbances are the cause of the pain of peptic ulcer is that our observations show that gastric or sphincteric motor disturbances

12. Hurst, A. F.: Sensibility of the Alimentary Tract, London, 1911, p. 47.

are almost invariably associated with the pain. But our observations do not furnish conclusive proof of the truth of this theory, and for this reason it must be admitted that the causal relation of motor phenomena to the pain of peptic ulcer remains problematical.

From the clinical standpoint the most important feature of the work here presented is considered to be the fact that the usual disappearance of abnormal motor phenomena occurring simultaneously with the cessation of pain gives an objective means of judging the effects of therapeutic measures.

CLINICAL OBSERVATIONS ON THE CAPILLARY CIRCULATION *

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The direct observation of the capillary circulation in disease has long been the aim of many workers, interested in a variety of clinical and experimental problems. It is evident that the rest of the cardiovascular system exists only to regulate the blood flow through the capillaries, for here takes place the exchange of gases necessary for internal respiration and the exchange of materials necessary for metabolism. Any attempt to measure cardiovascular function is an indirect attempt to measure the efficiency of the capillary circulation. For example, blood pressure determinations are supposed to give some indication of the peripheral blood flow, but as will be seen later, blood pressure is often a poor index of the state of the capillary circulation. Much work has been done experimentally upon so called capillary poisons, such as arsenic, etc., stimulating a clinical interest in many of the acute intoxications, especially those accompanied by skin reactions, such as occur after arsphenamin injections, diphtheria antitoxin, also occasionally after the injection of foreign proteins. In acute infections, such as influenza, the sudden collapse is often attributed to a capillary intoxication. The disturbances of water balance in conditions like acute nephritis are by some supposed to be dependent upon an alteration of the permeability of capillary endothelium. In traumatic shock there may be stasis of blood in the capillaries, as Cannon [1] and his co-workers have shown. Disturbances of blood flow in arteriosclerosis, in gangrene of the extremities, in various functional nervous diseases, such as Raynaud's diseases, in fact, any condition altering the nutrition of a tissue must have some vital relation to the capillary circulation. It is thus evident that a direct view of the circulation in this most important part of the vascular system might be of some clinical value.

Experimentally, investigation on the capillary circulation began soon after the microscope came into use. Malpighi observed blood flow in the mesentery and bladder of the frog in 1686; Leeuwenhoek observed it in the tail of the fish and in the bat's wing; Cowper studied it in the mesentery of the rabbit. During the last century, investigation was centered particularly upon the contractility of capillaries and its control.

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* This work was made possible by the clinical facilities offered by the Cleveland City Hospital.

1. Cannon, et al.: Nature of Wound Shock. Blood in Shock and Hemorrhage, J. A. M. A. **70**:526 (Feb. 23) 611 (March 2) 1918.

The names of Strickler, Golubew, Tarschanoff and the classical paper of Roy and Brown [2] in 1879 mark this period. Steinach and Kahn [3] in 1903, Krogh [4] in 1919, Hooker [5] in 1920 have contributed to this subject. An excellent review of the experimental work on capillaries was made recently by Hooker.[6]

Most of the animal observations have been made upon translucent tissues. The difficulties of similar observations in man are obvious. Ophthalmologists have carefully studied the condition of the vessels in the cornea and retina by means of various special microscopes. Augstein [7] observed in pannus the development of new corneal vessels by budding and branching, while Kraupa [8] observed the anastomosis of papillary veins, and also described the development of granular blood flow in arteriosclerosis and other conditions; and Streiff [9] saw changes in blood flow in vessels at the limbus due to nephritis and other conditions.

In 1874, Hueter,[10] by means of reflected light observed the vessels on the inner border of the lower lip, calling his method cheiloangioskopie. While he described stasis due to mechanical pressure, and experimented with the effects of applying various solutions, his results were indefinite.

Recently, Weiss,[11] standardized a method for the observation of the skin capillaries at the ends of the fingers and toes. Many years before, Spalteholz had shown that whole organs could be made translucent by reflected light, if they were immersed in a transparent oil. Lombard,[12] in 1912, working in Von Frey's laboratory applied this principle to the observation of capillaries at the fingertips in man, and made this obser-

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2. Roy and Brown: Blood Pressure and Its Variations in the Arterioles, Capillaries and Smaller Veins, J. Physiol. **2**:323, 1879.

3. Steinach and Kahn: Echte Kontractilität u. motorische Innervation der Haut-Kapillaren, Arch. f. d. ges Physiol. **97**:105, 1903.

4. Krogh: Studies on Capillariomotor Mechanism, J. Physiol. **53**:399, 1920; **52**:457, 1919.

5. Hooker: Functional Activity of Capillaries and Venules, Am. J. Physiol. **54**:30, 1920.

6. Hooker: Evidence of Functional Activity on the Part of Capillaries and Venules, Physiol. Rev. **1**:112, 1921.

7. Augstein: Gefäss-studien an der Hornhaut u. Iris, Ztschr. f. Augenh. **8**: 1902.

8. Kraupa: Die Anastomosen an Papillen u. Netzhautvenen, Arch. f. Augenh. **78**: 1915.

9. Streiff: Zur methodischen Untersuchund der Blutzirculation in der Nahe des Hornhautrandes, Klin. Monatsbl. f. Augenh., p. 395, 1914.

10. Hueter: Chielangioskopie, Zentralbl. f. d. med. Wissen., pp. 225, 241, 1879; Deutsch. Ztschr. f. Chir. **4**:105, 1874.

11. Weiss: Beobachtungen u. mikrophotographische Darstellung der Hautkapillaren der ledenden Menschen, Deutsch. Arch. f. klin. Med. **3**:119, 1916.

12. Lombard: Blood Pressure in the Arterioles, Capillaries and Smaller Veins of the Human Skin, Am. J. Physiol. **29**:355, 1912.

vation the basis of a method for measuring capillary pressure. Recently this method was modified by Hooker.[13] Weiss [14] together with Jürgensen [15] and other German workers have made numerous observations on the capillaries in a variety of clinical conditions. Niekau [16] by means of a special instrument extended the observations to other skin areas. Many records of the capillary picture were made in cardiovascular conditions, nephritis, diabetes, skin diseases, etc., and on this basis they have constructed tentatively rather definite capillary records corresponding to a variety of diseases. However, as Müller [14] states, it is too soon as yet to say what clinical value the method has. Normal standards for age, sex, climate, etc., have not been made. Many other difficulties will be pointed out later. A clinical method to be of value must be susceptible of wide use by a variety of observers under different conditions and with fairly constant results. It is with the hope of stimulating a trial of this method rather than of drawing any very definite conclusions that our observations are recorded.

Anatomic Basis.—Spalteholz [17] showed that the capillaries of skin are end capillaries, that is, they do not anastamose but form single terminal loops, each having a distinct arterial and a distinct venous limb. Each papilla of the skin is supplied by a single capillary loop which runs at right angles to the skin surface. However, as we approach areas where the skin ends, such as the base of the finger and toe nails, the long axis of the capillary tends to become more and more parallel with the skin, so that in cases with a well developed undisturbed cuticle, the loop runs in practically the same plane as the skin surface. Thus, looking down vertically upon the skin surface, at the junction of the cuticle and nail, we see the capillary loop in practically its entire length, while in other localities only the top of loop is seen. Figures 1 and 2, diagrams from Spalteholz, will make this clear.

The Method.—The finger, one with a well developed cuticle, is placed on the stage of an ordinary microscope, so that the junction of cuticle and nail is under the objective. This region of the finger is coated with any transparent oil (we have used liquid petrolatum). An electric light is then focused so as to strike the part observed at an angle of about 45 degrees. The light, a 50-100 watt, is enclosed in a conical hood with a convex lens inserted at the apex for condensing

13. Hooker and Danzer: Capillary Blood Pressure in Man, Am. J. Physiol. **52**:136, 1920.

14. Weiss and Müller: Ueber Beobachtung der Hautkapillaren u. ihre klinische Bedeutung, München. med. Wchnschr. **64**:609, 1917.

15. Jürgensen: Microscopic Study of the Capillary Circulation, Deutsch. Arch. f. klin. Med. **132**:140, 1920.

16. Niekau: Beobachtungen mit dem Hautkapillarmikroskop, Deutsch. Arch. f. klin. Med. **132**:301, 1920.

17. Spalteholz: Handatlas der Anatomie des Menschen **3**.

the light. The hood is mounted on a ring stand. We used an ordinary Bausch and Lomb microscope with a 16 mm. objective and 5 × and 10 × oculars, giving a magnification of from fifty to one hundred times. Others have used lower magnification. The patient's arm can be put on pillows and braced by sandbags and to steady the observed finger, one can hold it lightly or have it inserted in a mould made of tin or a dental mould. Several minor precautions made the observation clearer, namely (1) the skin should be clean and dry, (2) it is best to observe a finger where the cuticle has not been recently cut or disturbed, (3) at times there are disturbing light reflexes from the

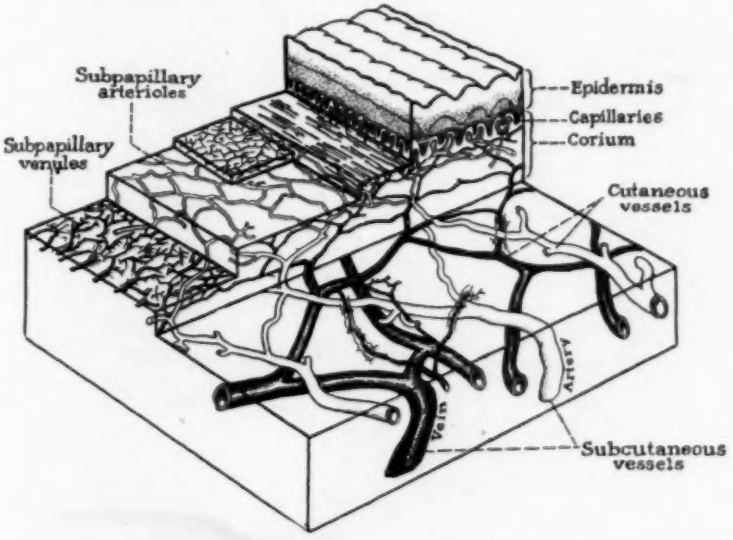

Fig. 1.—(After Spalteholz).

skin which can be diminished by changing the angle of the light or covering part of the convex lens in front of the light. One does not obtain a clear view in every case, for where the epidermis is thick and rough, and the cuticle is ragged, a good observation is impossible. Obviously it can not be used upon colored patients. Futhermore the patient must cooperate in holding his arm and fingers quiet, for much pressure upon the finger can not be used in restraint, because the blood flow will be altered.

Normal Appearance.—Wtih a clear view, just proximal to the junction of the cuticle and the nail, one sees a row of ten to twenty hairpin shaped loops, red upon a light orange background. Often more rows of capillaries are seen, running parallel to the first but with the indi-

vidual loops becoming shorter, that is, the more perpendicular to the skin, the more proximal the row. Observation should be focused on the most distal row of capillaries. It will be seen that each loop has a shorter, narrower limb (the arterial limb), and a thicker, longer limb (the venous limb), and that they are joined by a short connecting limb usually about the same thickness as the venous limb. Usually, no flow is at first visible but upon closer observation, in most cases, a rapid, steady, continuous stream will be seen going from the arterial to the venous side. The view is sometimes improved by the use of a green screen. Sometimes the individual blood cells are discernible, but more often not. In thin skinned individuals the subpapillary venules can be seen running at right angles to the loops, and occasionally the venous limbs can be traced down to this point. The subpapillary arterioles lie deeper, and are not visible except in infants. Normally, no pulsation of the field or the individual capillaries is

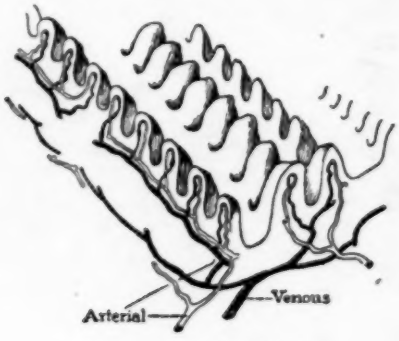

Fig. 2.—(After Spalteholz).

seen. The individual loops vary considerably in their contour. The arterial and venous limbs are fairly straight but in normal individuals they are often quite tortuous. Some may appear darker in color than others, probably due to differences in depth. There is also some variation in size.

For a systematic observation, the following points should be recorded:

1. The number of capillaries in the first row, increased or decreased over normal.
2. Color of background.
3. Size of capillaries, relative size and thickness of arterial limb, venous limb, and connecting limb.
4. Contour of capillaries.
5. Degree of capillary filling.

6. Presence of blood flow, speed and character of flow.
7. Pulsation of individual capillary or of field.

The interpretation of any single case may be wrought with many difficulties. No standards have been established for age, sex, race, climate, etc. It is a method not susceptible of accurate quantitative measurements, so that the personal equation of the observer enters into the conclusions very greatly. Furthermore, the observations are limited to skin capillaries, which are larger and because of their heat and water regulating function, capable of greater change due to external conditions than are capillaries elsewhere. We also know that

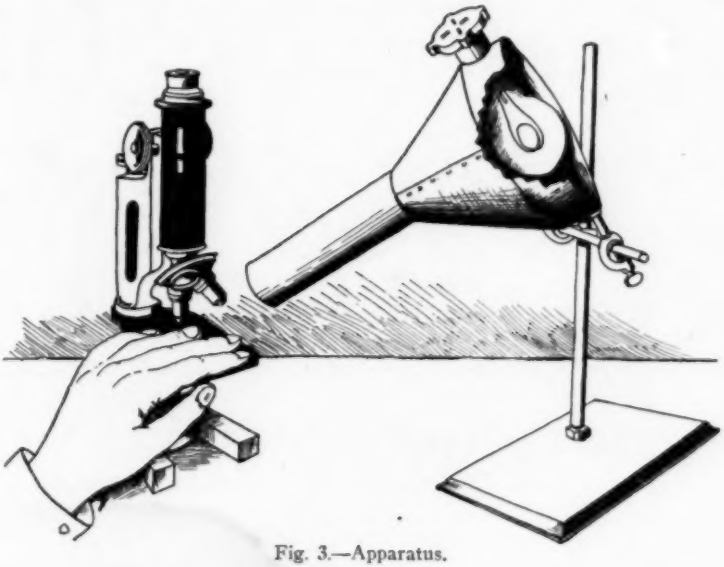

Fig. 3.—Apparatus.

capillary systems vary in form, depending upon function, thus differing in lung, intestine, pancreas, kidney, spleen, etc.[18] For these reasons, the skin capillary picture will never be a short cut diagnostic procedure, but may be at its best only of some diagnostic aid when taken with the rest of the clinical picture.

Variations Due to Age and Sex.—In observing over 200 cases, persons ranging in age from 1 day to 70 years, very few variations could be detected due to age alone. The skin vessels can be seen very clearly in young infants due to their thin epidermis. About half of the infants showed very small capillary loops with a diffuse

18. Nagel: Handbuch d. Physiologie **1**:760.

network of larger vessels, such as one sees in a frog's web, while in other cases there were long thin loops, rather widely separated, with arterial, venous and connecting limbs of the same caliber. The arterial and venous limbs were widely separated and very long and were traceable to the underlying subpapillary arterioles and venules. Occasionally, short buds were seen branching off of the limbs, suggesting the beginning of other loops. Probably, the large loops are not real capillaries, but only the subpapillary vessels. The blood flow in infants is steady and rapid. Why some infants show capillary loops and others do not is inexplicable to us. At the age of six months most of the cases observed showed very little difference from the adult condition. In older individuals there is a tendency for the capillaries to become more tortuous, but tortuosity is frequently seen in young people without any demonstrable cause. No differences attributable to sex were observed.

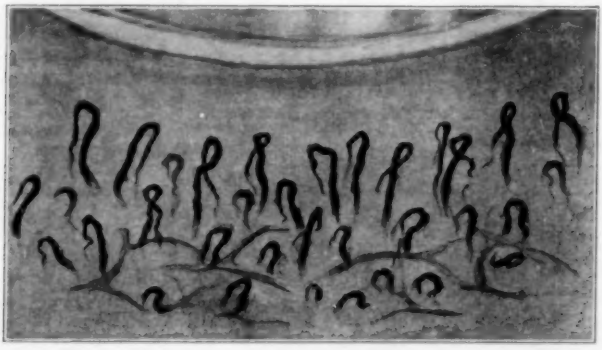

Fig. 4.—Normal.

Vasomotor Reactions.—It has long been a disputed point as to whether variations occur in the caliber of capillaries independent of changes in the arterioles and venules. An excellent review of the experimental work on this subject has recently been made by Hooker [9] and space will not permit us to repeat it here. Suffice it to say that overwhelming proof has not yet been assembled in favor of the independent contractility of capillaries. We have tried to observe the effects of mechanical stimulation as is done in the "tache" test of Marie, which was used clinically by Müller,[19] and Cotton, Slede and Lewis.[20] However, the field was so clouded by the stroke of the needle that no unequivocal observations could be made.

19. Müller: Deutsch. Ztschr. f. Nervenh. **48**:413, 1913.
20. Cotton, Slade, Lewis: Contractile Power of Capillaries, Heart **6**:227, 1915.

Weiss claims to have seen the arterial end of a capillary contract while observing a man with "vasomotor" spasm in the arm. He also quotes C. E. Weiss as having seen a spasm of the smaller retinal vessels (capillaries?) in a patient with a transient amaurosis.

Stewart,[21] by measuring the blood flow in the hand, showed that reflex stimuli such as heat and cold, when applied to the other hand, markedly altered the blood flow to the part, presumably by the reflex action causing constriction and dilatation of the arterioles. We have repeated these experiments by observing the capillaries of the finger in one hand while immersing the other hand in either cold or warm water. Cold caused a momentary increase in the velocity of the blood flow which gave way soon to a marked slowing, amounting sometimes to complete stasis. The capillaries appeared slightly wider and more full of blood. The appearance of increase in width was probably largely due to a slowing of the current, thus decreasing the axial stream, rather than to an active dilatation. This stasis was not permanent, but there was an intermittent alteration of the speed of the blood flow until gradually at the end of some minutes the flow became almost normal again. With heat the flow became much more rapid but the capillaries did not change in contour.

In explaining the reaction to cold one can conceive of the slow capillary flow being caused in any one of three ways. The velocity of the stream could be decreased by arterial constriction diminishing the intake; a contraction of the venules increasing the resistance to the outflow; and finally, a dilatation of the capillaries themselves. Arterial constriction by itself, however, could not cause the capillaries to be as full as they were in these cases; venous constriction alone could retard the flow, and in the absence of a decreased intake, as from arterial constriction, the venous pressure would not have to be very high in order to cause almost complete stasis. Briscoe,[22] investigated the capillary and venous pressures in patients with irritable hearts. Many of these patients habitually had cold cyanotic hands and others were very susceptible to cold, their hands becoming blue and cold upon short exposure. In the first group of cases it was found that the venous pressure was slightly raised, while the capillary pressure was markedly elevated. In the second group the vasomotor reflex experiments were tried and upon putting one hand in cold water while observing the other hand there was a marked rise in capillary pressure and a slight rise in venous pressure, and the venules on the back of the hand were observed to decrease in size. These phenomena were supposed to be

21. Stewart: Studies on the Circulation in Man, Heart **3**:76, 1912.
22. Briscoe: Observations on Capillary and Venous Pressure, Heart **7**:35, 1918.

due to simultaneous contraction of arterioles and venules. In our experiments capillary dilatation by itself could hardly be the cause of the slowed flow because the capillaries were only slightly dilated, but at the same time they were definitely redder, that is, more full of blood. Consequently, the most plausible explanation of reflex capillary stasis is a simultaneous contraction of arterioles and venules. The application of this to the cyanotic mucous membranes, ear tips, finger tips, etc., occurring upon exposure to cold is apparent, as it is also to the local asphyxia in Raynaud's disease.

Occasionally, as Jürgensen [23] stated, in the course of an observation some of the capillaries suddenly became obliterated and then a moment later filled up again while the other capillaries in the field did not change. Many explanations for this have been offered. Jürgensen thinks that there are precapillary arterial-venous anastomoses which are under control of the central nervous system and this sudden blotting out of the capillaries is due to the shuting off of the blood through these vessels which have been suddenly opened and closed by reflex action. We have no evidence which bears on this point. Variations in the rate of blood flow without any change in the capillary contour were observed in normal individuals, but were more frequent in patients with cardiovascular disease. These changes were probably dependent on a variation in tone of the supplying arterioles, because they appeared simultaneously in contiguous groups of capillaries, they were more frequent in cases with hypertonus, and they were not accompanied by any demonstrable change in the contour of the capillaries.

Shock and Hemorrhage.—It will be necessary to review a few of the recent experimental findings in shock in order to form a basis for the interpretation of the capillary observations. For a long time it has been assumed, and more recently it has been proven by Gasser and Erlanger [24] and also by Lee,[25] that there is a reduction in the effective blood volume in traumatic shock. The question of the "lost" blood or "exemia" has been vigorously investigated. Inasmuch as repeated experiments have eliminated the arteries and veins, attention was directed to the capillary area as the blood reservoir.

During the war, Cannon [1] and his co-workers showed that in patients with shock the red blood count of the capillary blood was much higher than that of the venous blood. Dale and Laidlaw [26] by the injec-

23. Jürgensen: Mikrokapillar Beobachtungen u. Puls der kleinsten Gefässe, Ztschr. f. klin. Med. **86**:410, 1918.

24. Gasser and Erlanger: Plasma Volume and Alkaline Reserve in Shock, Am. J. Physiol. **50**:104, 1919.

25. Lee: Field Observations on Blood Volume in Shock and Hemorrhage, Am. J. M. Sc. **158**:570, 1919.

26. Dale and Laidlaw: Histamin Shock, J. Physiol. **52**:355, 1918.

tion of histamin produced a condition very similar to traumatic shock, and by exhaustive experiments they seem to have proven that the important factor in this condition is an endothelial intoxication with capillary stasis and increased permeability, causing a marked exudation of fluid into the tissues. Following this work, Bayliss [27] and others have attempted to prove that shock is chemical in its nature, that is, that some product of traumatized or poorly metabolized tissue causes an endothelial intoxication with the production of a shock-like condition. Aub and Wu,[28] in a few experiments, by measuring the blood gas in arterial and venous bloods, tended to show that there is stasis in the peripheral circulation in cases of experimental shock produced by trauma. However, the result of all this work is difficult to evaluate, for although it is evident that there is a reduction in the effective blood volume, and capillary stasis, it has not been definitely proved that this is the initiating and not a secondary phenomenon. Much controversy has ranged over the condition of the vasomotor center in shock. Erlanger, Gesell and Gasser [29] in studies on secondary shock produced by exposure and manipulation of intestines, partial occlusion of the vena cava and partial occlusion of the thoracic aorta, showed that the vasomotor center retains its tone during the development of shock. At necropsy, there was intense capillary congestion, especially in the intestinal area. These authors [30] believed that the slow flow induced by the vasoconstriction caused a clumping of corpuscles in the capillaries and veneules, thus choking and dilating these vessels causing transudation into the tissues and the diminution of the effective blood volume. These phenomena could not be limited to the portal area because shock could be produced in eviscerated animals. Seelig and Joseph [31] also proved that the vasomotor center was tonic until late in shock. Gesell,[32] in experiments on volume flow through the submaxillary gland, showed that a relatively small reduction in blood volume, as by a small hemorrhage, caused a relatively large reduction in volume flow. This was due to vasoconstriction. A simultaneous constriction of arterioles and venules could cause a marked capillary stasis. It became

27. Bayliss: Intravenous Injection in Wound Shock, 1918.

28. Aub and Wu: Studies in Experimental Traumatic Shock, Am. J. Physiol. **54**:416, 1920.

29. Erlanger, Gesell and Gasser: Studies in Secondary Traumatic Shock, Am. J. Physiol. **49**:89, 1919.

30. Erlanger and Gasser: Treatment of Traumatic Shock, Ann. Surg. **68**: 389, 1919.

31. Seelig and Joseph: The Vasoconstrictor Center During the Development of Shock, J. Lab. & Clin. M. **1**:283, 1916.

32. Gesell: Factors Controlling Volume Flow of Blood, Am. J. Physiol. **47**:468, 1919.

33. Gesell: Studies in Secondary Traumatic Shock, Am. J. Physiol. **49**:90, 1920.

evident during the war that hemorrhage plays a part in producing traumatic shock, or in hastening it, and this may be due to the vaso-constriction induced.

Clinically, traumatic shock is recognized by the group of symptoms, consisting of low blood pressure—grayish pallor—mental stupor—rapid, small pulse—rapid, shallow respiration and usually subnormal temperature. During the war, Cowell [34] called shock primary, if these symptoms followed immediately on the trauma, and secondary, if they developed gradually, without primary shock, or if the primary shock were recovered from to some extent and then followed by the more permanent condition characterized by the symptoms.

REPORT OF CASES

These three cases would probably fall under the head of primary traumatic shock:

CASE 1.—E. L., male, aged 23 years, admitted Jan. 8, 1921. About one hour before admission the patient had been struck by a train.

Physical Examination.—Temperature, 38 C.; pulse, 140, small volume; respiration, 30, shallow; blood pressure, systolic, 80; diastolic, not obtainable. Patient unconscious, grayish pallor. External wounds on scalp and body. Pupils: contracted, reacted slightly to light, other reflexes showed nothing abnormal. Capillary examination: (1) Increased in number; (2) capillaries full, and dark red in color; (3) contour—connecting and venous limbs relatively wide, as compared to arterial limb; (4) background, light orange; (5) blood flow—markedly slowed and stream somewhat segmented; (6) no pulsation of capillaries or of field.

CASE 2.—J. C., aged 20 years, admitted April 15, 1921. Crushed between freight cars, about one-half hour before admission.

Physical Examination.—Temperature, 38 C.; pulse, 140, small volume; respiration, 38; blood pressure, systolic, 85; diastolic, 50. Patient conscious, pale. General rigidity and tenderness of abdomen, shifting dulness in flank, liver dulness not obliterated.

Operation revealed a rather large amount of blood in the peritoneal cavity, caused by the tearing of the mesentery for about six inches of the ileum. Resection of about one foot of the ileum, with lateral anastomosis. Patient died the next day.

Capillary examination: (1) Slight increase in number; (2) connecting and venous limbs relatively full; (3) capillaries, dark red; (4) field, light orange; (5) flow, slow; (6) no pulsation of capillaries or field.

These cases, clinically, are comparable to cases of primary traumatic shock. There was a definitely slowed capillary circulation and the capillaries appeared full. From the discussion in the previous section upon vaso-motor reactions, it is evident that the capillary stagnation could be due either to capillary dilatation or to a simultaneous contraction of arterioles and venules. Cardiac failure could hardly be a factor because there were no other signs of cardiac decompensation,

34. Cowell: Initiation of Wound Shock, J. A. M. A. **70**:607 (March 2) 1918.

such as distension of the jugular veins, enlargement of the liver, oedema, etc. Unfortunately, capillary and venous red blood counts were not made on these cases. The next case because of repeated observations may throw some light on the causative mechanism.

CASE 3.—R. W., male, aged 43 years, admitted March 11, 1921. Patient had shot himself in the abdomen about fifteen minutes previous to admission.

Physical Examination.—Temperature, 37 C.; pulse, 100, small volume; respiration, 26; blood pressure, systolic, 100; diastolic, 70. Patient conscious, pale. Abdomen slightly rigid in epigastrium. Gunshot wound through epigastrium.

Capillary examination: (1) Number increased; (2) capillaries very red and full; (3) contour, nothing remarkable; (4) flow, very slow, almost complete stasis in some loops; (5) background, dark orange. Red blood counts of the capillary and venous bloods at this time showed: (1) Capillary red blood corpuscles, 6,200,000; (2) venous red blood corpuscles, 3,776,000. The examination was repeated forty-five minutes later, the patient having had morphin, ¼ grain, fifteen minutes before. Pulse, 80, larger volume than before; respiration, 26, unchanged; blood pressure, systolic, 110, diastolic, 70. Capillary examination: (1) Capillary number, same; (2) capillaries not so full or so dark in color; (3) contour about the same; (4) field lighter; (5) flow, faster than before. Blood counts at this time: capillary, 5,210,000; venous, 5,576,000.

Operation revealed a gunshot wound of the liver with moderate amount of hemorrhage. Patient seemed in good condition upon leaving operating room. This patient presented a picture of mild traumatic shock. There was marked retardation of capillary flow. Yet on the administration of morphin, and external heat, within forty-five minutes his systollic blood pressure had risen from 100 to 110, his pulse had become fuller and his capillary flow had become almost normal. The slowed peripheral circulation could hardly be due to an endothelial intoxication causing a capillary relaxation, because of the quick recovery, but was much more likely due to a vasoconstriction which was relaxed by morphin. However, we are aware of the fact, that we were only examining a small portion of the skin capillaries, and local effects due to external conditions, such as temperature have not been excluded. We can only say that in observing a great many cases, and without paying attention to external conditions, we have not seen such marked capillary stagnation except when due to some clearly assignable cause, such as seen in cardiac decompensation. These observations present no evidence as to the cause of the vasoconstriction. The low pressure in the presence of a sound heart and vasoconstriction could only be explained by a diminution in the effective blood volume due to a sequestration of the blood in some part of the circulatory system and a loss of plasma in transudation through the vessel walls.

The more permanent condition of secondary traumatic shock resembles clinically the so-called surgical shock. Without definite cause, symptoms appear with a more gradual onset and a tendency to progress to a fatal ending. It is this type of shock which was studied so extensively during the war. This corresponds also to experimental shock.

Case 4.—L. R., female, aged 30 years, admitted Nov. 18, 1920. About twelve hours prior to admission, patient was seized with a sharp pain in the epigastrium, shortly after which vomiting began, and continued at frequent intervals. Colicky pains had continued. No bowel movement for twenty-four hours.

Physical Examination.—Temperature, 38 C.; pulse, 84, slow, full. Patient somewhat pale, tongue dry. Abdomen slightly distended, no rigidity, tenderness on the left, above the umbilicus. No peristaltic waves visible, increased peristalsis audible, no evidence of free fluid in abdomen. Repeated enemas with no results. Laparotomy: left rectus incision revealed almost all of the small intestines strangulated through an opening in the transverse mesocolon. Small intestine gangrenous except for about six inches near cecum. Ends of small intestine were stitched to abdominal wall. Patient was returned to bed in a condition of shock with a grayish pallor, cold perspiration, pulse 144, small volume. Temperature, 38 C.; respiration, 44, shallow; blood pressure, systolic, 75; diastolic not obtainable.

Capillary examination: (1) Background, purplish hue; (2) increased number; (3) capillaries showed narrow arterial limbs with wide connecting limb; venous limbs slightly widened; (4) capillaries, bluish red; (5) complete stasis.

In this rather typical case of surgical shock, there was complete capillary stasis, the connceting limb appeared definitely widened in relation to rather short and small arterial and venous limbs, and the capillary blood appeared suboxygenated.

Thus, the evidence of capillary stasis was much more marked than in the preceding cases. Of course, the point of most interest is whether the capillary widening was primary or whether it was secondary to a capillary stasis due to vasoconstriction, and which being prolonged caused a deficient metabolism of the tissues with the piling up of carbon dioxid and other metabolites, and subsequent capillary dilatation. All that we can maintain in this case of shock is that by direct observation there was complete stasis in the skin capillaries and the connecting limb of the capillaries was widened. The globular massing of corpuscles mentioned by Erlanger was not seen in any of these cases of shock.

Collapse in Septicemia.—It is a rather frequent clinical observation that some patients suffering from a general setpicemia go rather suddenly into a shocklike condition several hours before death. We have had the opportunity of observing a number of these cases soon after the onset of collapse. They presented the general picture of shock, low blood pressure, grayish pallor, at times cyanotic, semiconscious, perspiration, skin cold and clammy, low temperature, small fast pulse, shallow respiration.

Case 5.—*Puerperal Septicemia, General Peritonitis After Abortion.*—E. B., aged 30 years. On admission: Temperature, 41 C.; pulse, 140; respiration, 32. About twelve hours afterward the patient suddenly went into collapse with the general picture as above except that cyanosis was rather marked. Temperature, 37.4 C.; pulse, 160; respiration, 40; blood pressure, systolic, 75; diastolic ?.

Capillaries: (1) Increased in number; (2) background, light; (3) capillaries full of blood, dark red; (4) venous and connecting limbs relatively wider

than arterial limb; (5) flow, very slow and intermittent with complete stasis in some capillaries. Venous red blood cells, 4,800,000; capillary red blood cells, 6,400,000. Capillary blood did not flow freely and was very dark in color. Patient died about three hours after this observation.

CASE 6.—*Puerperal Septicemia, General Peritonitis Following Abortion.*—M. B., aged 22 years. General picture of collapse: Temperature, 37 C.; pulse, 132; blood pressure, systolic 75; diastolic, 50.

Capillaries: (1) Background, light; (2) about normal number; (3) contour, nothing remarkable; (4) filled, but in granular and segmented fashion, the cells being clumped together with clear spaces between; (5) absolute stasis. Venous red blood cells, 4,124,000; capillary red blood cells, 4,544,000.

These two cases of septicemia had capillary stasis, without showing other evidence of cardiac decompensation. There are so many factors to consider in these cases, that at this time we can only submit the observations without offering any theoretic basis for them.

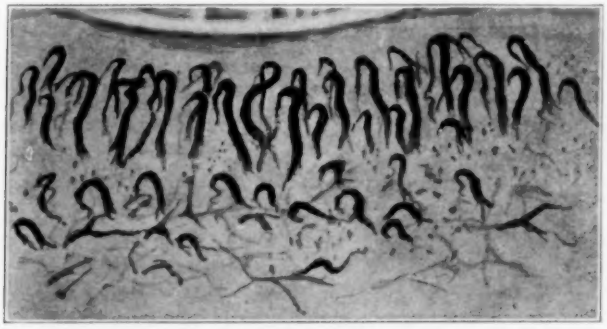

Fig. 5.—Shock.

Several cases of uncomplicated hemorrhage have been observed, all of them being cases of incomplete abortion of which the following is typical:

CASE 7.—S. S., aged 33 years, admitted April 29, 1921. The patient was about three months pregnant and several days previous to admission began to have vaginal bleeding. On the day of admission she had a severe hemorrhage and passed some clots.

Physical Examination.—Temperature, 38 C.; pulse, 128, small volume; respiration, 30, shallow. Blood pressure: systolic, 60; diastolic, 25. Patient was very pale, conscious and restless. Bleeding from vagina. Examination showed a partly retained placenta. Hemoglobin, 55 (Talquist); venous red blood cells, 1,840,000; capillary red blood cells, 2,108,000.

Capillary examination: (1) Decreased in number; (2) background very light, almost white; (3) capillaries poorly filled, appear granular due to clear spaces between blood cells. No dilatation; (4) capillary flow very slow and intermittent with varying speed.

The capillary was characterized by the granular appearance of the stream due to the anemia; and the slow capillary circulation was probably due to vaso-constriction resulting from the diminution in blood volume. The stasis, however, was not extreme as was evidenced by the red blood counts.

As was mentioned above, Gesell showed that a comparative small loss of blood volume as by hemorrhage could cause a large diminution in volume flow, because of vasoconstriction. Robertson and Bock,[35] in observation on the blood volume in soldiers who had had a hemorrhage, found that the diminution in blood volume was greater than the amount of the hemorrhage warranted. The red blood corpuscle count and hemoglobin determinations in capillary and venous blood showed that this was due to capillary stasis.

Cardiac Disturbances.—Decompensation: Weiss [14] and Jürgensen [15] made direct observations of the capillary circulation in many varieties of heart disease, and in all stages of decompensation. We have been able to confirm most of their findings. In well marked decompensation, the capillaries are increased in number, the arterial limb is small and narrow while the connecting limb and especially the venous limb are

Fig. 6.—Cardiac stasis.

wide and full. The flow is very slow. Sometimes there is complete stasis, and the blood flow is not steady, but the corpuscles appear rolled together, with clear spaces between. If the spaces are frequent, thus making the groups of cells small, the stream is called granular, and if the spaces are farther apart the stream is called segmented. Occasionally in complete stasis there is an intermittent retrograde movement from the venous toward the arterial limb. The background is very dark, probably due to stasis in the underlying venules. In mild cases of decompensation all that one may see are slightly widened venous and capillary limbs with slight slowing of the current and a granular or segmented stream. The German investigators claim that

35. Robertson and Bock: Blood Volume in Wounded Soldiers, J. Exper. M. 29:136, 1919.

signs of stasis may be seen in the capillaries before other clinical signs are present, for example, after acute infections which are liable to produce cardiac complications, they claim that the capillary picture of decompensation may precede other symptoms. We have not observed any such cases. However, we have observed several cases of recovery from a cardiac breakdown, which clinically seemed to be compensated, but in which capillary circulation was slowed, the stream was granular or segmented, and the venous limb was full and wide. It appeared to us that the complete picture of stasis in mitral disease appeared earlier, was more marked, and persisted longer than in aortic disease. One of the most marked cases observed was a man with tuberculous pericarditis with a large effusion. A direct view of the capillaries has seemed useful to us in a few cardionephritics. Especially when they present the well developed picture of edema, shortness of breath, etc., it is often difficult to decide readily whether the kidney or the heart is more at fault. For example, one case was observed, that of a man about 50 years of age, who had general anasarca, ascites and hydrothorax and was markedly short of breath. The capillaries showed only a slight slowing and no marked fulness of the venous limb. It was apparent that this man's clinical picture could not be entirely due to cardiac failure. Weiss [36] thought that he could measure cardiac function by putting a blood-pressure cuff on the arm and then observing the capillaries. His method was to raise the pressure in the cuff until the flow stopped, then to lower the pressure, and observe the point at which the stream started. He claimed that in normal individuals the stream started at a point from 5 to 10 m. below the stytolic pressure, while in cases with diminished cardiac "power," the flow would not start until the pressure was much lower. As Jürgensen points out, this method as a test of cardiac function has very little basis theoretically, and we have found it of no practical value.

Capillary Pulse: It is well recognized that a capillary pulse is a constant finding in aortic insufficiency, and that it is frequently observed in aortitis, arteriosclerosis, exophthalmic goiter, febrile disturbances, etc. However, clinically, it has not been studied intensively. Herz [37] by means of onygraphic pressure records together with radial pulse records concluded that what was called a capillary pulse was really a pulsation of the smaller arterioles and could be changed or made to disappear in many cases by influences such as changes of temperature. However, Glässner,[38] using the same methods, concluded

36. Weiss: Eine neue Methode zur Sufficienz-prüfung des Kreislaufs, Ztschr. f. exper. Path. u. Therap. **19**: 1918.

37. Herz: Wien. Klin. **6**:165, 1896.

38. Glässner: Klinische Untersuchungen über Kapillarplus, Deutsch. Arch. f. klin. Med. **97**:83, 1909.

that a capillary pulse was either central or peripheral in origin, central in aortic insufficiency, but peripheral, due to vascular changes, in other cases, such as arterio-sclerosis, nephritis, exophthalmic goiter, etc. As Jürgensen points out, in observing the capillaries in aortic insufficiency, the whole field seems to move in two planes; one at right angles to the microscope and the other in the same plane as the microscope; that is, the field moves horizontally and vertically. In the few cases which we observed, it also appeared as if the flow in the capillaries was actually pulsatile, although, due to the vertical movement, it is difficult to observe the blood flow continuously. Observations were made on cases of exophthalmic goiter, arteriosclerosis and neurasthenia, in which a capillary pulse was present, but the pulsation was only in the horizontal plane, and the blood stream in the capillaries was not pulsatile. So

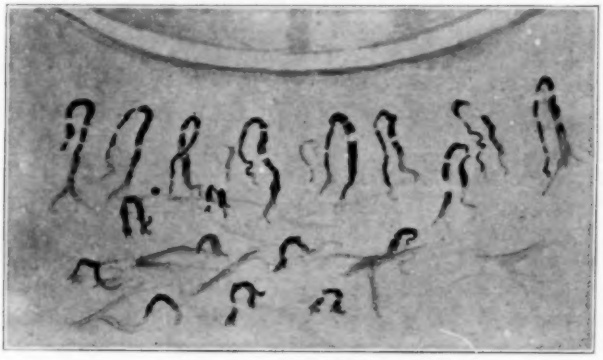

Fig. 7.—Anemia from hemorrhage.

this was definitely an arteriole pulsation and could be called a pseudo-capillary pulse. Jürgensen saw capillary pulsations in cases of syphilitic aortitis, but unfortunately all the patients with this disease, available to us, were colored.

Chronic Interstitial Nephritis and Hypertension.—Cases of hypertension, either with or without other signs of nephritis, are often puzzling because of the varying picture which they may present. Given two patients with the same blood pressure, one may be perfectly comfortable and the other may present all sorts of symptoms, such as aphasia, anaurosis, headaches, dizziness, etc. Various focal symptoms have been explained upon the basis of small hemorrhages, or arterial spasm. Again, in some cases, the blood pressure may be reduced without producing any symptoms, while in other cases a slight reduction in the pressure is attended by marked disturbances.

The capillary picture may possibly throw some light on these phenomena:

CASE 8.—A. F., aged 41 years, female, admitted Feb. 14, 1921. For several months the patient had dizzy spells and headache, and black spots before the eyes. More recently she had frequent vomiting spells. For several days she had slight continuous vaginal bleeding. The day before admission she had a convulsion.

Physical Examination.—There was evidence of cardiac hypertrophy, but no edema. Pulse was 100 and small volume. The eye-grounds showed a marked albuminuric retinitis. Blood pressure: systolic, 240; diastolic, 160. Urine: albumin +++, many casts.

Capillary examination: (1) Slight increase in number; (2) background, light; (3) capillaries poorly filled, appear granular. All limbs thin and of about the same width. Rather marked tortuosity; (4) flow, intermittent, stream being very swift for a moment, then it would suddenly stop completely.

When observed the next day the systolic blood pressure was 202, and the capillary picture was unchanged. An amylnitrite pearl was given and the systolic pressure dropped to 170, the capillary flow became steady, and there was a marked pseudo-capillary pulsation. However, in the course of five minutes the pressure was back to its previous level and the capillary flow resumed its original character.

It was seen that the capillaries were poorly filled and the flow was intermittent. This must have been due to arterial hypertonus, because first the capillaries were poorly filled, as one would expect with arteriole contraction, and second, the flow became better under amyl nitrite. In confirmation of this point, Kraus found a lowering of the capillary pressure along with a rise of the arterial pressure in many cases of hypertonus. Evidently, many of the patient's symptoms were due to poor capillary circulation, and in such a case reduction of the blood pressure would seem to be rational therapy. We have observed other cases of hypertension in which the flow was steady and continuous, and these patients had few symptoms.

In chronic interstitial nephritis the capillaries usually have long thin arterial and venous limbs with a slightly wider connecting limb. The flow depends on the degree of arterial tonus.

Arteriosclerosis.—In marked cases of arteriosclerosis the arterial and venous limbs are elongated, thin and tortuous and show a very characteristic formation of small loops off of the main limbs. These little loops look like buds and, by some, are supposed to represent an attempt at the formation of anastomosis or of new capillaries. Those loops do not appear in all cases of arteriosclerosis, and in our observations bear little relation to the amount of arteriosclerosis in the palpable arteries. The most marked cases of "budding" which we have seen, were in two cases of club fingers, with little demonstrable arteriosclerosis. However, other cases of club fingers did not show the "buds." Their significance is not clear to us.

Capillaritis.—The terms endothelial intoxication and capillary poison, have been used lately in relation to a variety of phenomena. Weiss [39] gives a rather definite picture for this capillary disturbance which he calls capillaritis. The capillary has short, narrow, arterial and venous limbs and a widely distended connecting limb. He described this in cases of acute nephritis, especially in children, in scarlet fever, occasionally before eruption. We have observed no cases of scarlet fever and only one case of acute nephritis, this in an adult whose capillaries showed no marked change. However, it was thought one should be able to obtain some evidence of capillary intoxication in cases of mercury and arsenic poisoning. In one case of fatal mercuric chlorid poisoning, with complete anuria, no capillary change was observed. Several cases were observed, showing salivation and gingivitis due to mercurial therapy, and with one exception there was nothing of note in the capillaries. This patient, age 20 years, had received a great deal

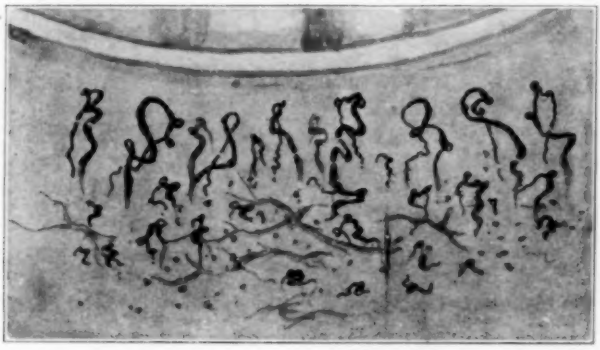

Fig. 8.—Arteriosclerosis.

of mercury by injection and inunction. He was markedly salivated and his gums were very swollen and sore. He also complained of anorexia and bachache. The capillaries appeared increased in number, very red, with short arterial and venous limbs, and relatively broad connecting limb. Blood flow was steady and moderately fast. Presumably, this is what Weiss describes as a capillaritis. However, the same picture was observed in three other cases, one, a patient with Banti's disease, and the others apparently normal individuals. Two cases of arsphenamin intoxication were observed, one an acute reaction with an eruption, fever, and edema; the other, a chronic case of jaundice, nausea and vomiting, and neither showed any capillary change.

39. Weiss: Beobachtung über Veränderung der Haut-kapillaren bei Exanthem, München. med. Wchnschr. **65**: 1918. Das Verhalten der Haut-kapillaren bei akuter Nephritis, München. med. Wchnschr. **63**:925, 1916.

Other Diseases.—Unfortunately, we have not had the opportunity of observing many conditions which might show something of interest; vasomotor disturbances, such as Raynaud's disease, erythromelalgia, disturbances in various kinds of paralysis, etc. Niekau,[16] by means of a special microscope designed by Müller observed the skin in locations other than the finger tips. He studied various skin diseases, such as psoriasis, also some of the acute exanthemata.

Some work has been done on capillary flow in diseases of infancy, such as exudative diathesis. Observations would be of interest in the acute intoxications in which Merriot [40] has shown by blood flow measurements that the peripheral circulation is slowed. Thus, there are many clinical branches in which a direct examination of the capillaries might be of interest.

CONCLUSION

While the observations in this series of cases might lead one to draw certain general conclusions as to circulatory condition in shock, in cardiac conditions, etc., one must be very careful in his deductions. The method is not a quantitative one, and only a few of the capillaries of a most labile part of the circulatory system are being observed. Consequently the reports of a large number of cases by different observers must be awaited before we can evaluate the method. However, because of the corroboration of the clinical picture and of certain experimental work, one has some faith in observations of a capillary stasis in shock, the capillary picture in cardiac decompensation, the poor capillary flow in some cases of hypertension, and the different pictures of a capillary pulse.

It is hoped that other workers will be interested in making similar observations.

SUMMARY

1. Observations on the capillary circulation in many clinical conditions were made by Lombard's method.

2. The effect of reflex vasomotor stimuli on the capillary circulation were observed, corroborating the blood flow experiments of Stewart.

3. In three cases of primary traumatic shock and one case of surgical shock, stasis was observed in the skin capillaries.

4. Capillary stasis was observed in several cases of septicemia, which had a sudden collapse.

5. Capillary stasis occurs in cardiac decompensation and may be of some value in differentiating the preponderant factor in cardiorenal diseases.

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40. Merriot: Some Phases of the Pathology of Nutrition in Infancy, Am. J. Dis. Child. **20**:461 (Nov.) 1920.

6. In some cases of hypertension, there is a granular, intermittent capillary flow.

7. A true capillary pulse can be differentiated from a pseudocapillary pulse.

8. Observations may be of value in diseases where an endothelial intoxication or capillaritis is suspected, but no conclusive observations on such cases were made in this series.[41]

Our thanks are due to Dr. L. J. Karnosh for the drawings. The sketches are semi-diagrammatic camera lucida drawings with a magnification of approximately × 70. In some cases they represent the composite picture of several cases.

41. The attention of the authors has just been directed to the fact that a sort of polemic has been going on in the German and Austrian journals between Weiss and Schur[42] regarding priority in the application of Lombard's method to the clinical observation of capillaries. We know nothing of the merits of the controversy.

42. Schur: Ueber Kapillar-beobachtung, Wien. klin. Wchnschr. **33**:928, 1920.

THE PROTEIN REQUIREMENT IN TUBERCULOSIS*

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In a previous communication,[1] which was concerned chiefly with the total energy transformations in tuberculosis, a few experiments were given dealing with the nitrogen minimum in this disease. It was thought to be desirable to extend these observations so as to include data, not only regarding the minimal level of protein metabolism, but as far as possible to throw light on the optimal quantity with which to supply patients suffering from pulmonary tuberculosis.

Because of its intimate bearing on the problem of finding the optimal protein requirement for such patients, the knowledge acquired concerning the basal metabolism was supplemented by experiments on the effect of protein food upon the heat production. Further experiments were made[2] in which the action of all the foodstuffs was studied, not only on the metabolism, but on the pulmonary ventilation as well.

Studies of the protein metabolism in this disease, made up to 1903, have been compiled by Ott.[3] Up to that time no attempts seem to have been made to find the protein minimum in tuberculosis.

From 1888 to the present time there has been a great development of our knowledge of the size of the normal quota of protein for wear and tear. The general method for determining this has been to provide the experimental subject with a diet poor in protein (from 1 to 3 gm. nitrogen), but with an adequate supply of non-nitrogenous foods. Under these conditions, in normal men, the protein metabolism is reduced to the minimum which is necessary to cover the daily wear and tear of the protein containing organs and tissues. For ready reference the results of the more important of these experiments have been summarized in Table 8. More recently investigations of a similar character have been made to determine to

* From the Russell Sage Institute of Pathology, in affiliation with the Second Medical (Cornell) Division of Bellevue Hospital, New York, and from the Pathological Department, Bellevue Hospital.

1. McCann, W. S., and Barr, D. P.: The Metabolism in Tuberculosis, Arch. Int. Med. **26**:663 (Nov.) 1920.

2. McCann, W. S.: The Effect of the Ingestion of Foodstuffs on the Respiratory Exchange in Pulmonary Tuberculosis, Arch. Int. Med. To be published.

3. Ott, A.: Die chemische Pathologie der Tuberculose. Berlin, 1903.

what extent this wear and tear quota is affected in various diseases. A number of these have been summarized in Table 9.

Considerable discussion has arisen in the literature as to the existence or nonexistence of a "toxic destruction" of protein. For instance, if the size of the wear and tear quota is found to be increased some authors maintain that the increase is due to the action of toxins in disease. Others hold that the protein metabolism is increased as part of a generally increased metabolism, and that in spite of this nitrogen equilibrium may be established if an adequate diet is given. Reference to the experiments of Kocher [4] will show that the wear and tear quota in typhoid is much increased. However, the experiments of Schaffer and Coleman [5] show beautifully that if adequate amounts of carbohydrate, especially, and fat are given in typhoid fever the body may be protected from protein loss. This question has been well reviewed by Rolland,[6] who finds that there is no toxic destruction of protein in the sense that the body can not be protected from protein loss if an adequate diet be given, although she admits the possibility that it may occur to a slight degree in cases with temperature about 40 C. Rolland studied four cases of tuberculosis, one of whom she was able to keep in nitrogen balance with a diet furnishing 47 calories per kilogram and 10.7 gm. nitrogen. In another case 1.6 gm. nitrogen were added to the body daily with 49 calories per kilogram and 9.6 gm. nitrogen in the diet. Two of her patients were in negative nitrogen balance, but in one of these an adequate number of calories was furnished. Kocher [4] also studied some patients with tuberculosis in two and three day experiments, of which the data are too meager to justify any conclusions.

A great deal of attention has been directed towards elevation of body temperature as a possible factor in the increased protein metabolism of acute infections. May [7] has shown that the carbohydrate metabolism is greatly increased in fever. A deficiency of glycogen rapidly occurs, and the body proteins are called upon to take a large share in the increased energy production. That this state of febrile inanition plays a great part in the increased protein destruction has been shown by the results of Schaffer and Coleman,[5] to which reference has already been made. Bearing on the influence of body tempera-

4. Kocher, R. A.: Ueber die Grösse des Eiweisszerfalls bei Fieber und bei Arbeitsleitstung. Deutsch. Arch. f. klin. Med. **115**:82, 1914.

5. Schaffer, P., and Coleman, W.: Protein Metabolism in Typhoid Fever, Arch. Int. Med. **4**:538 (Nov.) 1909.

6. Rolland, A.: Zur Frage des toxogenen Eiweisszerfalls im Fieber des Menchen, Deutsch. Arch. f. klin. Med. **107**:440, 1912.

7. May, R.: cit. v. Noorden's Handb. d. Path. d. Stoffwechsels. Berlin, p. 591, 1906.

ture upon the protein metabolism are the valuable experiments of Graham and Poulton,[8] who elevated body temperature artificially by means of baths. These authors found that a rise of body temperature to 104.3 F., (40.2 C.) does not by itself cause any breakdown of the protein of the body. If a diet of very high caloric value is taken, containing a large excess of carbohydrate but a minimal quantity of protein, nonnitrogenous substances supply the whole of the increased energy production set up by the high temperature.

For the best recent summaries of our present knowledge of the protein metabolism reference may be made to those of Lusk,[9] Cathcart[10] and Van Slyke.[11]

TECHNIC

The technic of the management of the metabolism ward, in which the patients were kept, has been described in a paper by Gephart and DuBois.[12] In regard to the manner of weighing food, recording it, calculating its composition and caloric value, and the collection of the excreta the plan of Gephart and DuBois has been strictly followed.

The preparation of diets which could be completely taken and retained by sick patients, especially the tuberculous, required the greatest skill and painstaking care, for which we are greatly indebted to the chief nurse, Miss Estelle Magill, and her three assistants, Miss Elsa Forter, Miss Doris Cutler, and Miss Florine Nelson.

The data regarding diets given in Tables 1 to 4 represent only food which was actually ingested by the patients. The chief source of error which may exist is in the loss of food in the vomitus. A note has been made in each case in which this occurred.

In determinations of the respiratory metabolism made on our patients the apparatus used was a Tissot spirometer, in which expired air was collected and measured, and from which samples were taken for analysis. The analyses were done with a modified Henderson-Haldane apparatus. The exact technic of these determinations is given in a previous communication.[2] The first four subjects, in Table 7, were studied in the respiration calorimeter.[1] The basal

8. Graham and Poulton: Influence of Temperature Upon Protein Metabolism, Quart. J. M. **6**:82, 1912.

9. Lusk, G.: The Science of Nutrition, Ed. 3, W. B. Saunders Company, Philadelphia, 1917. Especially Chapter XII, pp. 334-361.

10. Cathcart, E. P.: The Physiology of Protein Metabolism. Monographs on Biochemistry. Longmans, Green and Co., London, 1921.

11. Van Slyke, Donald D.: The Chemistry of the Proteins and their Relation to Disease, Oxford Medicine, Vol. I. Oxford Press, 1920.

12. Gephart, F. C., and DuBois, E. F.: The Organization of a Small Metabolism ward. Clinical Calorimetry, Third Paper, Arch. Int. Med. **15**:829 (July) 1915.

requirement of energy for each patient was calculated from the data of the metabolism observations, adding 10 per cent. to the observed heat production to cover the effect of the specific dynamic action of foodstuffs.

In separation of the feces carmine was given in perforated capsules. The separations were all made satisfactorily for periods varying from three to eight days, generally five days. The stools were preserved with formalin in a refrigerator until the period was complete. They were then mixed and sent to the laboratory where they were rubbed to homogeneity with alcohol containing 1 per cent. sulphuric acid. After drying on a water bath the dry weight was taken, and the stools ground to a fine powder and preserved in a tightly stoppered bottle. Nitrogen in the urine and stools was determined by the Kjeldahl method. These analyses were made by Miss Frances D. Rule.

CASE HISTORIES

CASE 1.—*Early Apical Tuberculosis with Hemorrhage.*—Hubert W., a negro aged 28 years, was admitted Nov. 3, 1920, on account of blood spitting. He had "felt fine" in the morning of day of admission and had gone to work as usual. A few minutes after starting work he had a severe fit of coughing lasting ten minutes, during which he spat up one half cupful of frothy blood. Coughing thereafter at frequent intervals produced more hemoptysis. With the cough there was a dull sense of soreness over sternum and precordium.

Up to this time his health had been excellent. While in Central America in 1911 he had malaria. Cardiorespiratory history was negative, except for the fact that he was subject to frequent colds, with headaches and neuralgic pains about the eyes. For this he habitually took "headache powders." Weight was constant at its maximum of 135 pounds up to admission, though one week after admission it was found to be 120 pounds.

On admission, examination of the patient was limited to the front of the chest, in which the findings were only those of dulness, bronchovesicular breathing over the left upper lobe. His hemoglobin was 85 per cent.; red blood corpuscles, 5,152,000; leukocytes 6,400 with a normal differential count. The urine was normal, except for an occasional hyalin cast. Blood Wassermann reaction was negative. Temperature range, from 98 to 100 F.; pulse, from 60 to 90; respirations, from 20 to 30. Hemoptysis continued until November 10. Several sputum examinations were made, but no tubercle bacilli could be demonstrated.

November 10, physical examination was negative except for the chest. Patient was well developed and well nourished. The chest was large and well formed. There was distinct limitation of motion on the left side. There was normal resonance, except over the left upper lobe from the third rib in front to the mid-scapula behind. Over the dull area breathing ranged from bronchovesicular to bronchial in quality. Fine râles were heard over a small area below the outer third of the clavicle. The heart was normal in size and position. There were no murmurs. The rate and rhythm were regular. Blood pressure, systolic, 122 mm., diastolic 100 mm.

Roentgenograms Nos. 80,942 and 80,943 showed evidence of thickening of the pleura of the left lung, with infiltration of the extreme left apex, with hypervascularization of the right upper lobe. Heart shadow normal. Tuberculosis.

Patient was observed in the metabolism ward from November 10 to November 24. Dietary measurements and excreta analyses are tabulated in Table 1 (See also Fig. 1).

Nov. 27, 1920: Basal metabolism determination. Tissot spirometer. Age, 28; height, 166.5 cm.; weight, 55.1 kg.; surface area, 1.60 sq. m.; temperature, 98.2 F.; pulse, 80; respirations, 20. Expired volume, liters per hour, S. T. P. D. = 57.95. Gas analysis—O_2 per cent. 18.54, 18.58. CO_2 per cent. 2.30, 2.33. R. Q. 0.94, calories per hour = 67.9. Metabolism, 107.5 per cent. average normal. Twenty-four hour heat production estimated $68 \times 24 = 1{,}632$ calories, basal energy requirement, $1{,}632 + 163 = 1{,}795$ calories.

TABLE 1.—CASE OF HUBERT W. (CASE 1)

Date, Nov. 1920	Calories per 24 Hrs.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Food N, Gm.	Urine N, Gm.	Fecal N, Gm.	Total N, Gm.	N Balance, Gm.	Weight, Kg.	Calories in Excess of Basal Requirement	Creatin per 24 Hrs. Mg.	Creatinin per 24 Hrs. Mg.
10	1,977	62.0	89.1	218.4	9.9	16.92	2.39	19.31	—9.4	55.51	182	119	1,836
11	1,950	63.5	90.6	206.5	10.2	8.40	2.39	10.79	—0.6	.....	155		
12	1,751	62.2	90.8	207.7	10.0	10.12	2.39	12.51	—2.5	55.19	(—44)	48	1,520
13	2,538	36.1	121.5	307.2	5.8	6.20	2.30*	8.50	—2.7	.....	743	3†	1,473
14	2,507	37.1	120.9	300.2	5.9	6.20	2.30	8.50	—2.6	.....	7..	12†	1,495
15	1,293	19.3	57.0	166.9	3.1	6.20	2.30	8.50	—5.4	55.16	(—502)	10†	1,445
16	2,390	27.7	112.4	300.2	4.4	6.20	2.30	8.50	—4.1	.....	596	8†	1,358
17	2,390	27.7	112.4	300.2	4.4	6.20	2.30	8.50	—4.1	55.29	596	†	1,400
18	2,500	34.3	109.3	327.6	5.5	4.77	2.30*	7.07	—1.6	.....	706		
19	2,601	38.6	110.0	351.3	6.2	5.20	2.30	7.50	—1.3	.....	806		
20	2,508	35.6	110.0	326.3	5.7	4.50	2.30	7.80	—2.1	56.41	713		
21	2,508	35.6	109.5	326.3	5.7	5.07	2.30	7.37	—1.7	.....	713		
22	2,390	27.7	112.4	300.2	4.4	4.11	2.30	6.41	—2.0	.....	595		
23	2,312	26.6	105.2	298.7	4.3	3.78	2.30	6.08	—1.8	.....	517		
24	2,469	27.7	120.9	300.2	4.4	3.96	2.30	6.26	—1.9	55.11	674		

* Fecal nitrogen estimated. Analyses made in Periods I and IV.
† Creatin-free diet.

Comment.—Examination of the data in Table 1 shows that the urinary nitrogen excretion did not fall as promptly in response to the reduction in food nitrogen as it did in the subsequent cases. The cause of the lag is not at once apparent. There was practically no fever (from 98 to 100 F.) during the two weeks of observation. There was no evidence of toxicity. The patient felt quite well. It it not unlikely that the source of the extra nitrogen was clotted blood retained in the lung and undergoing slow absorption.

The nitrogen loss in the feces was quite large throughout. There was no diarrhea. The diet was not of a bulky nature such as would ordinarily lead to poor utilization.

At the end of the period of observation the area of dulness over the left upper lobe was somewhat diminished below the clavicle. Breath sounds had a slightly higher pitch than normal and a somewhat prolonged expiration. No râles were heard.

Case 2.—*Acute Pneumonic Phthisis.*—Abraham M., an Arab, aged 21 years, was admitted Nov. 29, 1920, complaining of cough and pain in the chest. His illness began two months before admission with a severe "cold," cough persisted with expectoration. For two weeks prior to admission he had been expectorating blood.

His previous health was good, except for an attack of pneumonia (date not given), and an ischiorectal abscess, which he had before coming to America in 1920. He also had measles and typhoid fever (dates not given). He had an operation for hemorrhoids in 1917. His appetite was always poor, but he had no digestive disturbances until present illness. Venereal disease was denied. He smoked cigarettes excessively. Weight before present illness was 130 pounds. Four of his brothers died of tuberculosis.

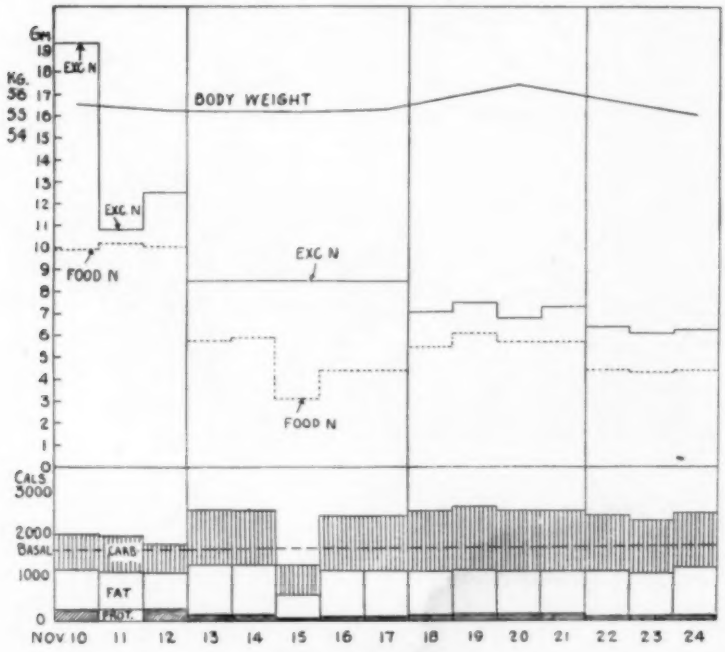

Fig. 1.—Hubert W.

From November 20 to 26 he was on the service of Dr. James Alexander Miller, on which the following examination was made:

General appearance: Poorly developed and poorly nourished colored Arabian male lying quietly in bed with rapid respirations and productive cough. The skin is hot, dry and shiny, with no visible cyanosis or rashes. Glands are not enlarged. Extremities show no edema, clubbing, but marked wasting. Reflexes: Knee jerks sluggish, Oppenheim and Babinski not obtained. The head is of normal contour. Hair, thick and curly. Eyes: Pupils dilated, react normally to light and accommodation. There is no nystagmus, strabismus or ptosis. Ears: No discharge or mastoid tenderness. Mouth: Teeth fairly good. Tongue coated. Pharynx injected. Neck: No rigidity, no thyroid enlargement. Thorax: Long and narrow. Retraction of both supraclavicular fossae. Expansion is

limited throughout the left side. Fremitus poor throughout and marked dulness and bronchovesicual breathing above the left second rib and angle of scapula. Below these there is bronchial breathing and pectoriloquy. There are numerous fine and moist râles throughout the left side. The right side is resonant with harsh breathing and increased whispered voice above the spine of the scapula. No definite râles were heard. Heart: Apex impulse in fifth left intercostal space. No enlargement, no thrills or murmurs. The pulmonary second sound is accentuated. Rate rapid, rhythm regular. Abdomen: Scaphoid, no areas of tenderness or rigidity. Liver and spleen not palpable.

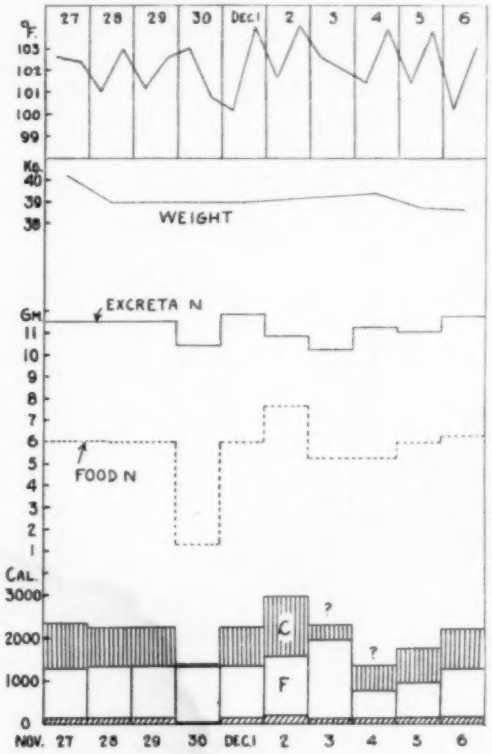

Fig. 2.—Ab. M.

A provisional diagnosis of acute pneumonic phthisis was made. Many tubercle bacilli were found in the sputum. Urine normal. Temperature: High with remissions, from 104 to 100 F. Pulse, from 100 to 120. Wassermann reaction negative.

November 26: Admitted to metabolism ward (See Table 2 for data regarding diet and excreta) (Fig. 2).

December 1: Passed *ascaris lumbricoides* in stool. Examination shows no other ova present than those of ascaris.

December 3: Leukocyte count, 15,800; eosinophils, 5 per cent.; lymphocytes, 3 per cent.; large mononuclears, 13 per cent.; transitionals, 1 per cent., polymorphonuclears, 78 per cent.

November 29: Basal metabolism determined. Height, 168 cm. Weight, 40 kg. Body surface area, 1.42 sq. meters. Temperature, 101.6 F. Volume expired. S. T. P. D.—57.85 liters. Gas analysis: CO_2 per cent. 2.17, 2.20. O_2 per cent. 18.42, 18.40. R. Q. = 0.824, calories per hour, 72.74. Metabolism 130 per cent. of average normal. Daily heat production (average temperature 101 F.) = 1,744 calories. Estimated basal requirement = 1,744 + 174 = 1,921 calories per diem.

The patient was observed in the metabolism ward from November 27 to December 6 inclusive. During this time he was extremely ill. It was with the greatest difficulty that he could be persuaded to take food. On three days vomiting occurred so that an unknown quantity of food was lost.

TABLE 2.—Abraham M. (Case 2.)

Date, Nov.-Dec., 1920	Total Calories per 24 Hours	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Food N, Gm.	Urine N, Gm.	Fecal N, Gm.	Total N, Gm.	N Balance, Gm.	Food Calories ÷ Basal Requirement	Body Weight, Kg.	Creatin, Mg. per Diem	Creatinin, Mg. per Diem	Remarks
27	2,360	37.3	123.8	257.6	6.0	10.83	0.70	11.53	−5.5	+440†	.....	71*	962	Period I
28	2,497	36.8	128.7	280.4	5.9	10.83	0.70	11.53	−5.6	+577	40.25	71*	962	
29	2,497	36.8	128.7	280.4	5.9	10.83	0.70	11.53	−5.6	+577	.....	71*	962	
30	1,375	8.4	140.0	9.6	1.3	9.72	0.70	10.42	−9.1	−545	.....	211*	987	Vomited
1	2,497	36.8	128.7	280.4	5.9	11.13	0.70	11.83	−5.9	+577	38.99	227*	997	
2	2,947	47.2	148.9	333.9	7.6	9.97	0.80	10.77	−3.2	+1,027	35.15	....	...	Period II
3	2,300	32.4	196.0	83.9	5.2	9.43	0.80	10.23	−5.0	+380	.....	....	...	Vomited
4	1,360	32.6	70.7	138.6	5.2	10.40	0.80	11.20	−6.0	−560	39.39	....	...	Vomited
5	1,738	36.8	87.1	180.4	5.9	10.20	0.80	11.00	−5.1	−182	38.70			
6	2,184	39.0	119.1	223.4	6.2	10.86	0.80	11.66	−5.5	+294	38.61			

* Creatin-free diet.
† Basal requirement estimated at 1,920 calories per diem.

The data regarding diet measurements and excreta analyses are shown in Table 2, and graphically in Figure 2. It will be seen that the urinary nitrogen figure at its lowest was almost double the food nitrogen, in spite of the fact that on all but three days the energy value of the food was in excess of the estimated basal requirement.

Of the ten cases in which the nitrogen metabolism has been studied by us, this one shows the highest protein metabolism. It is unique in our series, resembling much more closely the patient with croupous pneumonia studied by Kocher [4] (Table 9). This patient had the physical signs of a pneumonic consolidation, with tubercle bacilli in the sputum. It is not known to what extent other organisms entered into the production of the pneumonia.

This patient was the subject of an experiment to determine the specific dynamic action of fat, and its effect upon the pulmonary ventilation. The data of this experiment are to be found in a previous paper.[2]

CASE 3.—*Massive Bilateral Infiltration of Lungs with Multiple Excavations.*—Fred R., a porter, aged 41 years, was admitted Nov. 23, 1921, complaining that for three years he had had a chronic cough with progressive loss of weight and strength. He had never enjoyed good health. In 1917 he began to have a cough with a little sputum. He felt badly but continued to work fourteen hours a day up to February, 1920, when he was obliged to quit work because of weakness and shortness of breath. He then had three hemoptyses. He was admitted

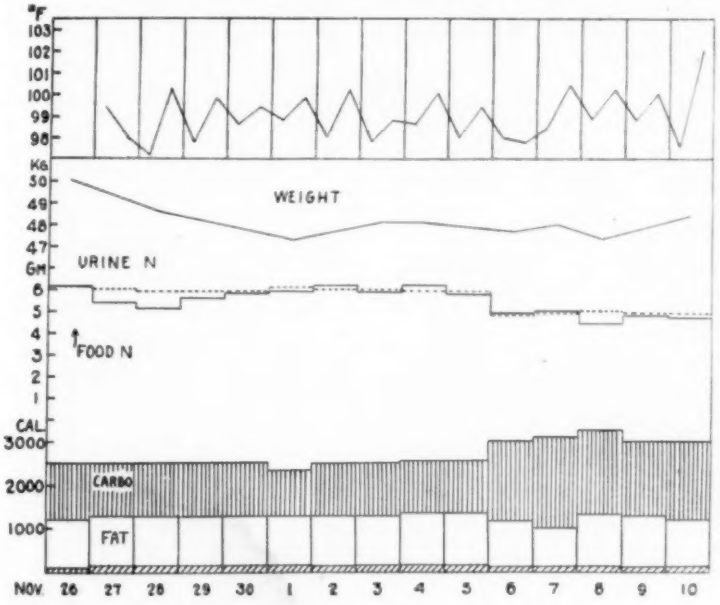

Fig. 3.—Fred R.

to the Seaview Hospital in April, 1920, and remained there until September, 1920. After his discharge he went to the country where he stayed until Nov. 15, 1920. Since his return to New York he has had attacks of "heart standing still," which brought him into the hospital. The past history is chiefly irrelevant. His best weight was 145 pounds, present weight 105 pounds. Two of his brothers are known to have tuberculosis.

Physical Examination.—Height, 167 cm., weight, 47 kg. Fairly well developed, emaciated, lips slightly cyanotic, respirations rapid but with no subjective distress. The head, eyes, ears, nose, mouth, throat and neck were normal.

Chest: There was marked emaciation with myoidema. There was marked limitation of the respiratory excursion on the right side, with supraclavicular retractions and of the lower right intercostal spaces. Both upper lobes were

dull, especially the right. The whole right chest was dull, front and back. The left lower chest was resonant, almost tympanitic. Over the whole chest numerous fine and coarse râles and rubs were heard. The breath sounds over the left upper lobe were harsh with prolonged expiration. Over the right upper lobe there were areas of amphoric breathing, elsewhere bronchial, and over the right lower lobe there was distant bronchial breathing.

Heart: Apex impulse was in the fifth intercostal space 11 cm. to the left of the midline. Rhythm regular. No murmurs heard. The pulmonary second sound was accentuated. Pulses synchronous, soft, and rapid. The vessels were not sclerosed. Blood pressure, systolic 85 mm. The abdomen was normal, except that the soft smooth liver edge was felt just below the costal margin.

TABLE 3.—Fred R.

Date, Nov.-Dec., 1929	Total Calories per Diem	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Food N, Gm.	Urine N, Gm.	Fecal N, Gm.	Total N, Gm.	N Balance, Gm.	Calories +/− Basal Requirement*	Creatin per 24 Hrs. Mg.	Creatinin per 24 Hrs. Mg.	Body Weight, Kg.	Remarks
26	2,524	26.1	130.0	317.2	4.2	6.14	1.12	7.26	−3.1	+454	0	966	50.00	Period I
27	2,524	37.2	128.8	286.2	6.0	5.37	1.12	6.49	−0.5	+454	3	982	.....	Creatin-free
28	2,497	36.8	128.7	280.4	5.9	5.09	1.12	6.21	−0.3	+427	0	957	48.56	diet
29	2,497	36.8	128.7	280.4	5.9	5.57	1.12	6.69	−0.8	+427	12	959		
30	2,497	36.8	128.7	280.4	5.9	5.79	1.12	6.91	−1.0	+427	20	885	.....	No urine lost
1	2,344	38.1	113.6	276.0	6.1	5.87	0.96	6.83	−0.7	+274	0	959	47.29	Period II
2	2,491	37.2	112.3	315.7	6.0	6.13	0.96	7.09	−1.1	+421				
3	2,502	37.4	112.4	318.2	6.0	5.86	0.96	6.82	−0.8	+432	..	...	48.08	
4	2,537	36.8	127.7	292.3	5.9	6.18	0.96	7.14	−1.2	+467	..	...	48.04	
5	2,537	36.8	127.7	292.3	5.9	5.83	0.96	6.79	−0.9	+467				
6	3,004	29.7	114.4	443.4	4.8	4.88	1.32	6.20	−1.4	+934	..	...	47.65	Period III
7	3,131	30.4	105.6	496.8	4.9	4.95	1.32	6.27	−1.4	+1,061	..	...	48.03	
8	3,277	31.0	129.1	475.5	5.0	4.40	1.32	5.72	−0.7	+1,207	..	...	47.30	
9	2,995	30.5	122.4	422.4	4.9	4.83	1.32	6.15	−1.3	+925	..	...	48.20	
10	2,955	30.5	118.1	422.4	4.9	4.70	1.32	6.02	−1.3	+885	..	...	48.35	
11	2,647	91.4	144.8	225.6	14.6	9.26	....	....	.....	.....	..	...	47.46	Period IV
12	(2,748)	70.8	148.1	263.6	11.3	9.09	....	....	.....	.....	..	...	47.96	Vomited
13	(3,239)	96.0	183.0	282.0	14.9	8.00	....	....	.....	.....	..	...	48.71	Vomited
14	(986)	34.4	50.4	91.8	5.5	....	....	....	.....	.....	..	...	48.83	Died

* Basal requirement 2,070 per diem.

Reflexes: All deep reflexes were exaggerated. There was an exhaustable bilateral patellar and ankle clonus. Plantar reflexes were normal. The neck was not stiff, and Kernig's sign was not elicited. Further examination showed no abnormalities.

The urine was normal. Many tubercle bacilli were found in the sputum. He was transferred to the metabolism ward November 26 and remained there until his death on December 14. His diet and excreta are shown in Table 3 and graphically in Figure 3.

His basal metabolism was determined December 2 and 11, using the Tissot spirometer. The effect of ingestion of protein food on the heat production and pulmonary ventilation was studied. These experiments are to be found in a previous paper.[2]

The basal metabolism was 12 per cent. above the average normal when the temperature was 98 F. It was 28 per cent. above normal when the temperature was 100 F., being 65.5 and 75.0 calories per hour, respectively. The elevation

of metabolism is believed to be due largely to the dyspnea. The basal heat production is estimated to be between 1,620 and 1,880 calories per diem., and the basal requirement 2,068 calories.

Referring to the data in Table 3 it will be seen that, while the urinary nitrogen fell practically to the level of ingested protein, there was a persistent loss of nitrogen amounting to about 1 gm. per diem. Assuming muscle to be about one fifth protein, this nitrogen loss would represent the equivalent of about 30 gm. muscle per diem or about 1 kg. per month.

On the afternoon of the last day of period 3 the temperature rose to 102 F. On the following day it was planned to raise the food intake to the equivalent of 4,000 calories, with 90 gm. protein. The patient was unable to take the entire amount. On the following day vomiting occurred, and the temperature continued to rise, with a marked increase in the pulse and respirations. The patient continued to grow worse. Late in the afternoon of December 14 the patient became very dyspneic, respirations from 50 to 60 per minute, pulse from 130 to 140. Death ensued on the night of December 14.

Necropsy showed massive infiltration of the right lung, with huge cavities but no erosion of vessels. The left lung showed extensive infiltration, with small cavities, but still contained considerable air. There was no gross evidence of a superimposed pneumonia.

CASE 4.—*Infiltration of Both Upper Lobes.*—John O'C., a porter, aged 49 years, admitted Dec. 3, 1920, complaining of pain in the right chest and lumbar region, cough and expectoration. His mother died of tuberculosis. He had been married twenty years, having five children living and well. He had been well until 1889, when he had some pulmonary trouble for which he was confined to bed for three months. After that he had a persistent cough. His general condition remained fairly good up to 1910 when he began to work at night. His weight which had been 170 pounds dropped to 150 pounds. In 1917 he developed a migratory arthritis which involved many joints, for which he was twice admitted to Bellevue Hospital. He had had a nystagmus all his life. He had many attacks of quinsy sore throat. He had had a persistent cough since 1889, with occasional streaks of blood in the sputum. No history of dyspnea, edema or night sweats until present illness. He had had frequent attacks of alcoholic gastritis. Appetite habitually good. Bowels constipated. Until present illness patient had nocturia, no dysuria or other urinary symptoms. Venereal disease was denied. Habits alcoholic. Weight: best, 170 pounds; 150 pounds in 1910; 133 pounds in 1917; present weight 110 pounds.

Present Illness.—Began in the middle of November, 1920, with pain over the whole front of the right chest and in the right lumbar region. There was considerable cough and some expectoration. The pain was increased by deep breathing. He remained at work one week in this condition and then was forced to spend the afternoons in bed. Growing worse he came to the hospital for admission.

Physical Examination.—Height, 174.3 cm., weight, 49.7 kg. Patient was a thin pale man appearing quite ill, lying flat in bed, very emaciated. There were dilated venules on the nose. The lips and finger tips were quite cyanotic. Respirations accelerated but not labored. Head: normal. Eyes: extraocular movements well performed. Patient unable to fix gaze because of a slight nystagmus, which is brought out strongly by looking to the left but not to the right, with the slow component to the left. Pupils equal and regular, react to light and accommodation. Ears and nose normal. Mouth: Teeth carious.

with many missing in the upper jaw. There was some pyorrhea. Tongue coated and tremulous. Pharynx congested. Tonsils normal. Larynx not examined, though voice was husky. Neck: Normal except for spasm of the right sternocleidomastoid muscle.

Thorax: of the long type with prominent sternum. There were marked supraclavicular retractions. Respiratory movements were shallow with greater restriction on the right side.

Lungs: both upper lobes were dull front and back. The left lower lobe showed little impairment of resonance. The right lower lobe was dull to

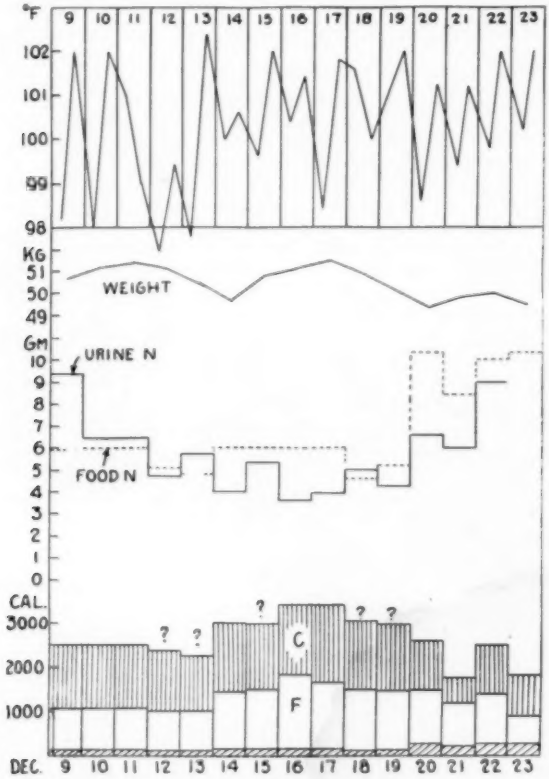

Fig. 4.—J. O'C. Question mark indicates an unknown amount of food lost in vomitus.

flat behind, extending almost to midline in front. Over this area there was diminished fremitus. Breath sounds over both upper lobes were bronchial, with clicking râles heard during quiet breathing and showers of fine râles during inspiration after coughing. At the right base the breath sounds are diminished or absent behind, with distant bronchovesicular breathing laterally. At the left base there was prolonged low pitched expiration of the emphysematous type.

Heart: Apex beat not seen and hardly felt. Apex dulness in the fifth intercostal space 8 cm. to the left of midline. The right border was 7.5 cm. to

the right in the third intercostal space. The rhythm is irregular (extrasystoles), rate rapid (90). No murmurs were heard. The arteries are somewhat thickened. The pulses equal and synchronous. Blood pressure: systolic, 128; diastolic, 100 mm.

Abdomen: Flat, rather rigid in the right upper quadrant. Liver and spleen were not felt. No tenderness or masses felt. Further examination revealed no abnormalities.

On admission the temperature was 101 F., and during the next five days it rose gradually to 102 F., in the afternoon. The urine was normal. The sputum contained many tubercle bacilli. Leukocytes, 9,900, with a normal differential count. Roentgen-ray examination (No. 84,275), December 14, showed evidence of narrowing of the intercostal spaces on the right side with marked thickening of the pleura of the right lung. There was peribronchial infiltration and agglutination of the foci in the upper parts of both pulmonic fields. The heart was slightly retracted to the right. A small effusion in the right costophrenic sinus could not be ruled out.

TABLE 4.—JOHN O'C

Date, Dec. 1920	Total Calories Food	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Food N. Gm.	Urine N. Gm.	Fecal N. Gm.	Total N. Gm.	N Balance, Gm.	Body Weight, Kg.	Remarks Calories ± Basal Requirement †
9	2,506	37.1	100.3	346.4	5.9	9.40	0.65	10.05	—4.2	50.71	+ 896 calories
10	2,503	37.3	100.9	343.3	6.0	6.44	0.65	7.09	—1.1	51.23	+ 893 calories
11	2,515	37.3	100.9	347.3	6.0	6.44	0.65	7.09	—1.1	51.41	+ 905 calories
12	2,371	31.8	94.6	331.9	5.1	4.71	0.65	5.36	—0.3	51.06	Vomited part of food
13	2,257	30.2	97.5	299.0	4.8	5.69	0.65	6.34	—1.5	50.50	Vomited part of food
14	3,004	37.2	189.2	381.9	6.0	4.00	0.53	4.53	+1.5	49.73	+ 1,394 calories
15	2,982	37.2	143.1	365.4	6.0	5.33	0.53	5.86	+0.1	50.80	Vomited at 11 p. m.
16	3,422	37.8	179.7	380.2	6.0	3.64	0.53	4.17	+1.8	51.10	+ 1,812 calories
17	3,427	37.6	161.4	432.3	6.0	3.94	0.53	4.47	+1.5	51.54	+ 1,817 calories
18	3,046	28.7	149.7	374.6	4.6	5.02	0.53	5.55	—1.0	50.89	Vomited part of food
19	2,984	32.3	143.7	380.7	5.2	4.26	0.53	4.79	+0.4	.....	Vomited part of food
20	2,601	64.4	132.1	270.2	10.3	6.58	1.0*	7.6	+2.7	49.33	
21	1,776	52.4	105.5	141.4	8.4	6.01	0.8*	6.8	+1.6	49.75	
22	2,503	62.7	123.6	267.6	10.0	8.95	1.0*	10.0	0	50.00	
23	1,823	64.3	63.6	236.1	10.3	....	....	.....	.....	49.50	

* Estimated at 10 per cent. of intake.
† Basal requirement estimated at 1,610 calories per diem.

Comment.—The patient was in the metabolism ward from December 9 to 20. The data regarding his diet and analyses of excreta are given in Table 4, and shown graphically with the temperature chart in Figure 4.

His basal metabolism was determined on two occasions, using the Tissot spirometer. December 14, with a temperature of 100.8 F., his metabolism was 3 per cent. above the average normal. December 23, it was exactly normal with a temperature of 100.6 F. The heat production was 62 and 61 calories per hour, respectively, on the two occasions. The basal heat production for twenty-four hours is 1,464 calories. Adding 10 per cent. for the specific dynamic action of food the basal requirement is estimated at 1,610 calories.

An experiment was done to study the effect of a small protein meal on the heat production and pulmonary ventilation. The experimental data of this and of the basal determinations are given in the preceding communication.[1]

Referring to the data in Table 4 it will be seen that the lowest urinary nitrogen excretion was reached December 16. This low figure was not obtained by reduction of the nitrogen intake to an extremely

low level, but rather by the ingestion of a large quantity of carbohydrate and fat. In spite of considerable fever, it was possible to achieve positive nitrogen balance by the ingestion of from 37 to 38 gm. protein when the total caloric value of the food was more than twice the estimated basal requirement of energy. The patient, however showed a marked tendency to digestive disturbances, and vomiting resulted frequently when attempts were made to increase the diet. The diet was much better taken when 60 or 65 gm. protein were given, and it will be seen that in this case nitrogen balance could be achieved by the ingestion of much less nonprotein food.

CASE 5.—*Infiltration, Right Upper and Middle Lobes, with Cavitation.*—Frank D., a plumber's helper, aged 17 years, was admitted Jan. 30, 1921, complaining of cough and weakness. Family history rather indefinite. Patient was raised in an orphanage. He had had measles, chickenpox and mumps. Each year he had attacks of severe sore throat. After a severe illness he was treated for one year for "heart trouble." He never had arthritis. He gave no history of any cardiorespiratory symptoms prior to present illness. Gastro-intestinal, urinary, and venereal history were negative. After leaving the orphanage he was employed at night doing very heavy work for two months. He became very much "run down." His weight fell from 125 to 97 pounds. He was out of work for a month, after which he found that he was too weak to work. He was then supported by another boy from the orphanage, who could allow him only $0.40 a day for food. For two months before admission he coughed, at first slightly, later severely with yellowish sputum. Three weeks before admission he had become so weak he remained in bed. Two weeks later he coughed up about one and one half ounces of blood.

Physical Examination.—Height, 165.5 cm., weight, 43 kg. A thin pale weak looking boy lying quietly in bed without respiratory embarrassment. No abnormalities were found other than those in the thorax.

Thorax: The clavicles were prominent, supraclavicular fossae well marked, especially of the right side. Respiratory excursion more limited on the right side.

Lungs: Both apices were dull, on the right side from the second rib to midscapula, on the left above the clavicle and spine of scapula. Over both dull areas the breath sounds were modified, bronchovesicular to bronchial, with many crepitant and subcrepitant râles. Resonance and breath sounds over the lower lobes were normal.

Heart: Apex beat, somewhat diffuse, was seen in the fifth intercostal space inside the nipple line. The area of dulness extends to the left 7.5 cm. in the fifth space and to the right 2.5 cm. in the third space. No murmurs were heard. The rate was rapid. There was a respiratory arrhythmia. The pulmonary second sound was accentuated. Pulses soft, rapid, equal and synchronous. Blood pressure, systolic 98 mm., and diastolic 70 mm.

On admission the temperature was 101 F.; pulse, 100; respirations, 24. The urine was normal. Tubercle bacilli were present in the sputum. Blood examination showed: hemoglobin, 79 per cent.; red blood cells, 4,320,000; leukocytes, 10,700 with 31 per cent. lymphocytes.

Roentgen-ray examination (No. 89,021) showed a localized area of peribronchial infiltration at the right upper lobe. There was considerable production of fibrous tissue with the presence of a cavity between the first and second ribs. There were also several foci of peribronchial infiltration in the middle lobe of the right lung.

The basal metabolism was determined with the Tissot apparatus Feb. 4, 1921. Height, 165.5 cm., weight, 43.24 kg. Volume expired, S. T. P. D., 363.1 liters per hour. Gas analysis: CO_2 per cent. 3.10; 3.11; O_2 per cent. 17.69, 17.72. R. Q. =

0.945. Calories per hour = 58.6. Calories per twenty-four hours = 1,406. The metabolism was 5 per cent. below the average normal for his age. The basal requirement, allowing 10 per cent. for specific dynamic action, was 1,547 calories per diem. The subject was not very suitable for respiration experi-

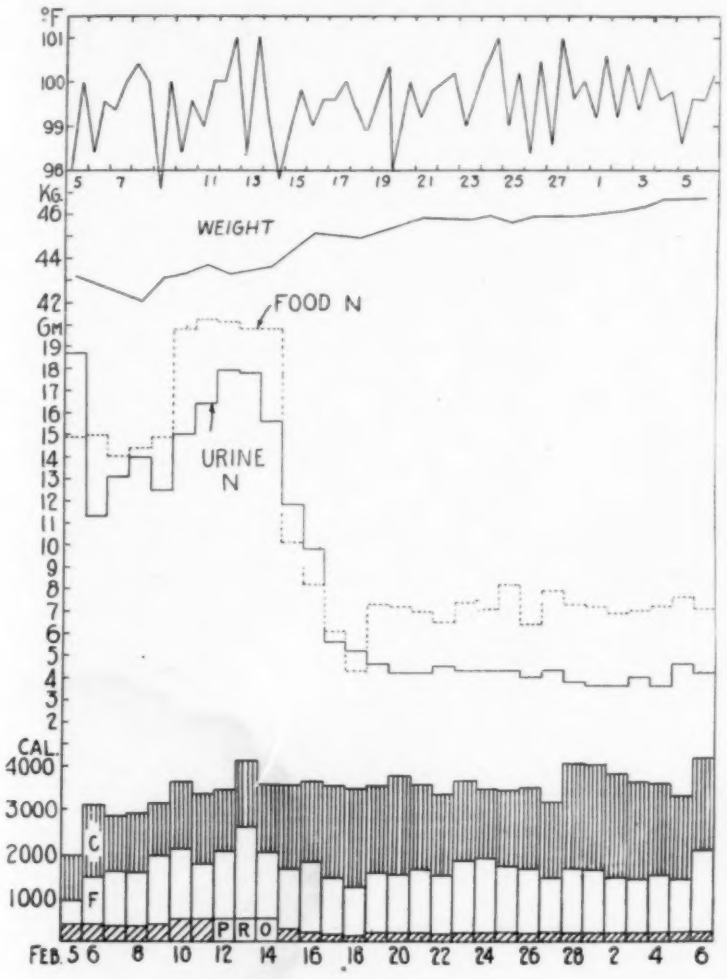

Fig. 5.—Frank D.

ments because of a persistent tendency to overventilate, which produced "Auspumpung" of carbon dioxid.

March 5 the metabolism was again determined. The weight was greater, 46.7 kg. Calories per hour 61.0 The metabolism was 4 per cent. below the average normal. Basal requirement = 1,610 calories.

He was observed in the metabolism ward from February 5 to March 7, 1921. The data regarding his diet and analyses of excreta are shown in Table 5, and graphically in Figure 5.

TABLE 5.—Frank D.

Date, Feb.-March, 1921	Total Calories Food	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Food N, Gm.	Urine N, Gm.	Fecal N, Gm.	Total N, Gm.	N Balance, Gm.	Calories ± Basal Requirement † *	Body Weight, Kg.
5	1,969	93.0	59.4	252.6	14.9	18.65	1.32	19.97	−5.1	+422†	43.2
6	3,101	93.8	116.2	398.7	15.0	11.31	1.32	12.63	+2.4	+1,554	
7	2,863	87.4	133.1	369.1	14.0	13.06	1.32	14.38	−0.4	+1,316	42.4
8	2,906	89.9	129.8	324.4	14.4	13.95	1.32	15.27	−0.9	+1,359	42.08
9	3,141	93.0	168.9	289.9	14.9	12.45	1.32	13.77	+1.1	+1,594	43.06
10	3,640	123.8	172.5	372.8	19.8	15.04	1.94	16.98	+2.8	+2,093†	43.28
11	3,377	126.2	133.3	395.2	20.2	16.43	1.94	18.37	+1.8	+1,830	43.77
12	3,455	125.7	166.9	338.5	20.1	17.86	1.94	19.80	+0.3	+1,908	43.33
13	4,115	124.0	225.0	369.2	19.8	17.77	1.94	19.71	+0.1	+2,568	
14	3,573	123.7	163.6	376.9	19.8	15.62	1.94	17.56	+2.2	+2,026	43.6
15	3,564	63.4	149.0	467.8	10.1	11.76	....	.....	.....	.....	44.39
16	3,634	51.1	171.9	445.1	8.2	9.81					
17	3,534	38.2	149.3	485.1	6.1	5.59					
18	3,470	26.6	121.4	519.9	4.3	5.23	....	.....	.....	.....	44.88
19	3,544	45.7	149.4	480.0	7.3	4.63	....	.....	.....	.....	45.17
20	3,783	44.8	143.8	551.7	7.2	4.22					
21	3,568	43.8	156.9	470.5	7.0	4.20	....	.....	.....	.....	45.8
22	3,344	40.4	143.0	450.8	6.5	4.52					
23	3,654	45.9	176.6	444.9	7.4	4.28	1.25	5.53	+1.9	+2,044*	45 60
24	3,460	44.1	181.9	387.0	7.1	4.31	1.25	5.56	+1.5	+1,850	45.89
25	3,434	51.0	159.4	425.1	8.2	4.28	1.25	5.53	+2.7	+1,824	45.65
26	3,489	39.8	159.8	448.8	6.4	3.98	1.25	5.23	+1.2	+1,879	45.85
27	3,156	49.1	134.7	415.2	7.9	4.37	1.25	5.62	+2.3	+1,546	
28	4,044	45.4	168.0	560.0	7.3	3.75	1.82	5.57	+1.7	+2,434*	45.85
1	4,008	45.0	155.3	580.6	7.2	3.57	1.82	5.39	+1.8	+2,398	
2	3,804	43.4	135.4	577.4	6.9	3.60	1.82	5.42	+1.5	+2,194	46.12
3	3,599	44.0	133.2	531.6	7.0	4.00	1.82	5.82	+1.2	+1,989	46 33
4	3,574	44.9	140.7	507.9	7.2	3.59	1.82	5.41	+1.8	+1,964	46.66
5	3,272	47.3	132.0	451.1	7.6	4.63	1.82	6.45	+1.1	+1,662	
6	4,150	44.6	202.3	508.7	7.1	4.22					

* Basal requirement estimated at 1,610 calories per diem.
† Basal requirement estimated at 1,547 calories per diem.

The observations were divided into five periods, in four of which the feces were separated and analyzed. In the first two periods the protein ingested was about 90 and 125 gm. per diem, respectively, with enough nonprotein calories to greatly exceed the requirement.

Period	Average Total Food Calories	Average Protein Daily, Gm.	Average Positive Nitrogen Balance
1 (last 4 days)	3,003	91	0.55
2	3,632	124.7	1.44
4	3,439	46	1.9
5	3,717	45	1.5

In period three the average daily calories ingested was 3,430. The food nitrogen was rapidly reduced to 4.3 gm., the urine nitrogen output falling gradually to 5.2 gm. At this point the food nitrogen intake was again raised to about 7 gm., (period 4), the urine nitrogen continuing to diminish.

CASE 6.—*Infiltration of Left Apex and Right Hilum, with Large Cavities.*—George R., a truck driver, aged 35 years, was admitted Jan. 4, 1921, complaining of fistula in ano, cough, loss of weight, and night sweats. Family history negative.

Past History.—General health not impaired until two months before admission. He had had fistula in ano for three years. In childhood he had measles only. No history of other infections, operations or injuries. He had never had a cough before July, 1920, and had never had dyspnea or edema. His appetite was always good and his bowels regular. There was never any pain on

FIGURE 2.—GEORGE R.

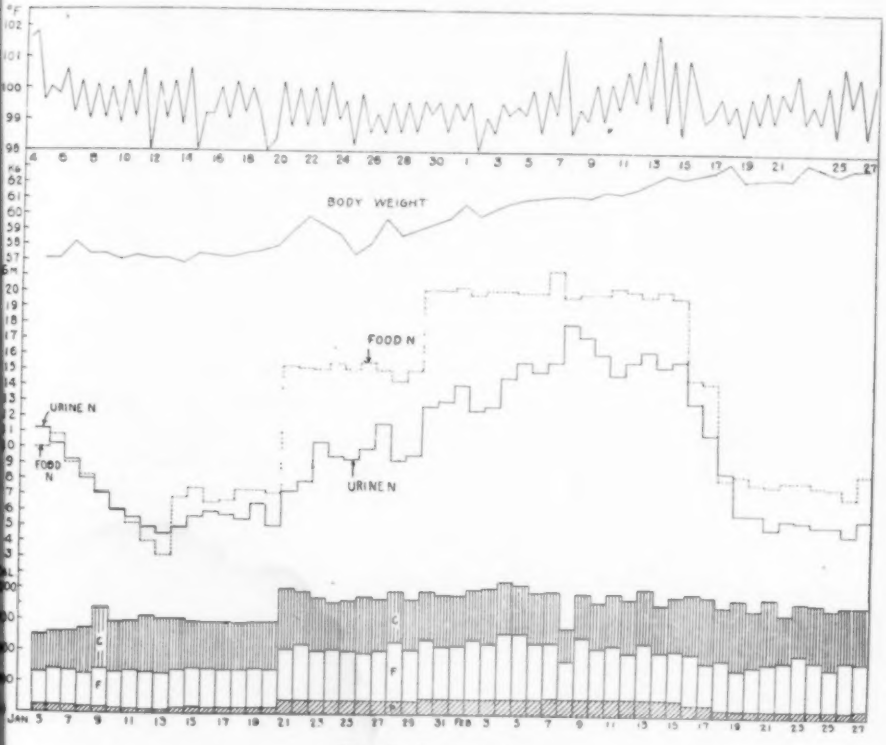

Fig. 6.—George R.

defecation though for three years he had had a fistula discharging pus. In January, 1920, a second fistula appeared, and in December, 1920, a third. He had never had any urinary symptoms. In 1908, he had a chancroid infection in the left inguinal glands. He had recently become a heavy drinker in spite of prohibition. His weight rose from 150 to 172 pounds in 1918, but fell again during the summer of 1920 to 144 pounds. Present weight 126 pounds.

Present Illness.—He began to cough in July, 1920. At first the cough was dry, later productive. In December, 1920, he began to notice small clots of blood in the sputum. He was never aware of afternoon fever, but about

TABLE 6.—GEORGE R. (CASE 6)

Date, Jan.-Feb. 1921	Total Calories Food	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Food N, Gm.	Urine N, Gm.	Fecal N, Gm.	Total N, Gm.	N Balance, Gm.	Calories ± Basal Requirement †	Body Weight, Kg.
5	2,508	62.6	112.5	294.0	10.0	11.20	....	....	.....	+724	57.1
6	2,597	67.8	122.2	288.6	10.8	10.22	....	....	.....	+813	57.1
7	2,581	56.1	120.5	300.0	9.0	9.16	....	....	.....	+797	58.1
8	2,760	51.3	111.3	369.6	8.2	8.00	....	....	.....	+976	57.4
9	3,375	44.4	134.9	472.7	7.1	7.08	....	....	.....	+1,591	
10	2,910	37.6	126.5	385.4	6.0	6.02	....	....	.....	+1,126	57.0
11	2,968	31.6	131.3	394.5	5.1	5.54	....	....	.....	+1,184	57.3
12	3,094	25.2	129.8	435.1	4.0	4.88	....	....	.....	+1,310	57.1
13	3,012	19.6	128.6	423.4	3.1	4.48	....	....	.....	+1,228	57.1
14	3,038	42.4	129.9	403.8	6.8	4 86	0.84	5.70	+1.1	+1,254	56.8
15	2,922	46.3	155.4	359.3	7.4	5.57	0.84	6.41	+1.0	+1,138	57.4
16	2,928	40.8	131.7	374.6	6.5	5.89	0.84	6.73	—0.2	+1,144	
17	2,919	41.5	129.1	377.6	6.6	5.69	0.84	6.53	+0.1	+1,135	57.2
18	2,877	45.5	129.5	362.7	7.3	5.42	0.84	6.26	+1.0	+1,093	57.5
19	2,906	45.7	134.2	358.8	7.3	6.35	0.84	7.19	+0.1	+1,122	57.6
20	2,983	44.6	128.4	379.5	7.1	5.05	0.84	5.89	+1.2	+1,149	57.9
21	4,013	94.8	180.1	475.3	15.2	7.24	*	8.8	+6.4	+2,229	
22	3,916	94.4	198.6	410.2	15.1	7.85	*	9.4	+5.7	+2,132	59.8
23	3,695	96.9	173.8	413.2	15.0	10.37	*	11.9	+3.1	+1,911	
24	3,556	96.0	179.0	365.3	15.4	9.50	*	11.0	+4.4	+1,772	58.7
25	3,631	94.2	174.3	396.0	15.1	9.27	*	10.8	+4.3	+1,847	57.4
26	3,744	96.7	166.0	439.9	15.5	10.05	*	11.6	+3.9	+1,960	58.1
27	3,674	98.7	177.6	399.5	15.0	11.61	*	13.1	+1.9	+1,890	59.5
28	3,918	89.5	208.0	394.3	14.3	9.26	*	10.7	+3.6	+2 134	58.6
29	3,659	94.0	180.3	389.6	15.0	9.59	*	11.1	+3.9	+1 875	
30	3,935	125.6	201.6	376.8	20.1	12.74	*	14.7	+5.4	+2,151	
31	3,824	125.4	179.5	400.2	20.1	13.05	*	15.1	+5.0	+2,040	59.8
1	3,796	127.1	182.2	385.4	20.3	14.08	*	16.1	+4.2	+2,011	60.6
2	3,976	123.8	204.1	383.0	19.8	12.53	*	14.5	+5.3	+2,192	59.9
3	4,042	125.7	189.8	429.8	20.1	12.73	*	14.7	+5.4	+2,258	60.4
4	4,249	125.6	223.7	408.3	20.1	14.56	*	16.6	+3.5	+2,465	60.8
5	4,169	125.2	227.3	376.0	20.0	15.56	*	17.6	+2.4	+2,385	61.0
6	3,897	124.3	191.5	391.8	20.0	15.03	*	17.0	+3.0	+2.113	
7	3,934	131.6	191.5	393.4	21.4	15.57	*	17.7	+3.7	+2,150	61.2
8	2,775	123.4	131.5	255.1	19.7	18.01	*	20.0	—0.3	+991	61.3
9	3,802	124.4	212.6	342.7	19.9	17.16	*	19.2	+0.7	+2,108	61.1
10	3,603	124.5	175.6	356.2	19.9	16.06	*	18.1	+1.8	+1,819	61.5
11	3,901	127.1	184.6	405.5	20.3	14.77	*	16.8	+3.5	+2,117	61.4
12	3,714	125.4	161.9	413.1	20.1	15.58	*	17.6	+2.5	+1,930	61.7
13	4,043	123.5	196.7	401.5	19.8	16.32	*	18.3	+1.5	+2,259	
14	3,567	125.9	162.9	374.2	20.1	15.30	*	17.3	+2.8	+1,783	62.6
15	3,781	1°3.9	168.2	416.8	19.7	15.69	*	17.7	+2.0	+1,997	62.4
16	3,806	90.6	174.6	463.7	14.5	13.00	*	14.5	0	+2,112	
17	3,818	89.1	145.0	513.1	14.3	10.98	*	12.4	+1.9	+2,084	62.8
18	3,511	50.4	173.6	412.2	8.1	8.58	*	9.4	—1.3	+1,727	63.4
19	3,729	52.4	137.3	545.5	8.4	5.93	*	6.8	+1.6	+1,945	62.3
20	3,399	49.5	151.2	436.7	7.9	5.90	*	6.7	+1.2	+1,615	
21	3,780	48.9	160.7	508.6	7.8	4.98	*	5.8	+2.0	+1,996	62.4
22	3,268	49.7	166.1	370.4	8.0	5.59	*	6.4	+1.6	+1,484	
23	3,626	49.9	192.4	398.0	8.0	5.45	*	6.3	+1.7	+1,842	63.4
24	3,580	48.0	169.1	443.6	7.7	5.23	*	6.0	+1.7	+1,805	63.1
25	3,428	47.7	146.1	456.8	7.6	5.22	*	6.0	+1.6	+1,644	62.7
26	3,525	43.6	175.9	417.1	7.0	4.56	*	5.3	+1.7	+1,741	63.1
27	3,527	53.1	164.1	434.8	8.5	5.00	*	6.5	+2.0	+1,743	

† Basal requirement estimated at 1,784 calories per diem.
* Fecal nitrogen estimated as 10 per cent. of food nitrogen.

July, 1920, night sweats began and had persisted. Appetite was still good, but patient was weak and short of breath on exertion.

Physical Examination.—Height, 163.5 cm.; weight, 57 kg. Patient was a young man with a full red face, sitting in bed, coughing occasionally, not acutely ill. He was fairly well nourished, with a rather flabby panniculus adiposus.

Head: Eyes, ears, and nose were normal. Mouth: Most of teeth present, moderate pyorrhea and dental caries. Pharynx and tonsils were normal. Neck normal. Thorax: Well formed and symmetrical. Respiratory excursions were equally limited.

Lungs: Both upper lobes were dull above the clavicles and behind as far as the midscapula. Anteriorly resonance was fairly good. Breath sounds were modified in the right axilla and along the border of the pectoral muscles there was bronchovesicular breathing and fine râles, and over the rest of the front there were moist and sonorous râles. Over both apices behind fine râles were heard on quiet breathing, chiefly on the left side. These râles were exaggerated by coughing. At the left apex just below the tip a squeaking post-tussive sound was heard. Breath sounds were bronchial or bronchovesicular with showers of fine râles.

Heart: Apex in fifth intercostal space 10 cm. to left of midline. Cardiac dulness extended to the left 11 cm. in the fifth space, and to the right 3 cm. in the third space. The sounds were of good quality, with no murmurs. Rhythm regular and rate slow. The pulmonary second sound was accentuated. Pulses soft and synchronous. Arteries normal. Blood pressure: systolic, 98; diastolic, 60.

Further examination revealed no other abnormalities, with the exception of the three fistulas which were situated close to the anus.

The sputum contained many tubercle bacilli. The *urine* was normal. Fluoroscopic examination showed pulmonary fields of equal size, diminished in illumination of both upper halves. There was a dense area running out from the hilus on the right side to the ribs. Above this area there was an intensely illuminated circular area which was thought not to be an antrum because lung markings could be seen through it. At the left apex there was seen to be an antrum, which was brought out by coughing, which was undoubtedly the source of the post-tussive sound heard in that region.

January 12: leukocyte count 10,000 with normal differential count.

January 18: leukocytes 15,000 with normal differential count; red blood cells, 4,200,000; hemoglobin, 75 per cent.

The patient was in the metabolism ward from January 5 to February 28. The diet record and the analyses of excreta are given in Table 6 and shown graphically in Figure 6.

The basal metabolism was determined January 26, and it was found to be 6 per cent. above the average normal, with a heat production of 67.6 calories per hour. The twenty-four hour basal heat production is estimated, therefore, to be 1,622 calories. If one adds 10 per cent. to this to allow for the specific dynamic of food the basal requirement equals 1,784 calories per diem.

An experiment was done to determine the effect of ingesting 350 gm. meat. The data for these observations is contained in a previous communication.[2]

Comment.—The data in Table 6 show that from January 5 to 13 the food nitrogen was reduced about 1 gm. daily, while during the same period the total caloric value of the diet was increased from 2,500 to about 3,000 calories. Under these circumstances the urine nitrogen decreased parallel with the food nitrogen until the latter reached 6.0 gm. per diem. After this point was reached the urinary nitrogen decreased more slowly until with a minimum ingestion of 3.1 gm. food nitrogen the urinary nitrogen was 4.48 gm.

For the remaining periods of observation the following summary is given:

Periods, Dates inclusive	Average Daily Calories in Food	Average Daily Protein in Food, Gm.	Average Daily Nitrogen Balance, Gm.
Jan. 14-20	2,932	43.8	+ 0.67
Jan. 21-29	3,756	94.1	+ 4.13
Jan. 30-Feb. 15	3,829	125.4	+ 3.1
Feb. 19-27	3,541	49.2	+ 1.67

It will be seen, therefore, that 43.8 gm. protein may be fairly taken as the minimum for this patient if a total of 2,900 calories per diem are ingested. It is quite clear that in this case there was no advantage to be had in giving more than 94 gm. protein per diem. Also in order to make large gains in nitrogen it was necessary to give a diet of which the energy value was about twice the basal energy requirement.

Entirely satisfactory gains in nitrogen and weight occurred during the last period, February 19 to 27. In this period 192 gm. was the maximum fat ingested, so that it was necessary to give between 370 and 545 gm. carbohydrate. From the standpoint of sparing the ventilation of the lungs this diet would not be satisfactory, because the increased breathing volume after taking this amount of carbohydrate would be greater than the effect of a diet containing more protein and less carbohydrate.

At the end of the period of observation the patient was transferred to the tuberculosis service. He had gained 14.8 kg. in weight, but in spite of the improved nutrition no improvement could be noted in his clinical condition.

DISCUSSION OF RESULTS

The Nitrogen Minimum.—Table 7 is a summary in which are arranged the data for each subject for the day on which the lowest urinary nitrogen excretion was noted. The first four subjects were studied in 1919-1920, and the complete data regarding them are to be found in the previous communication of McCann and Barr.[1] The total length of the observation in days is given. The number of the day selected for Table 7 is given for easier reference to the original data in preceding tables.

TABLE 7.—SUMMARY OF NITROGEN MINIMUM EXPERIMENTS IN TUBERCULOSIS

Name of Subject	Length of Experiment, Days	Day of Experiment	Total Calories in Food	Calories per Kg. Body Weight	Body Weight, Kg.	Food N, Gm.	Urine N, Gm.	Fecal N, Gm.	Total N, Gm.	Nitrogen Balance, Gm.	Food N per Kg., Gm.	Urine N per Kg., Gm.	Per Cent. Calories from Carbohydrate	Ratio of Total Calories to Basal Requirement
Charles G.*	24	16	2,091	40.1	52.2	2.8	4.3	(1.0)	(5.3)	(−2.5)	0.054	0.083	43	1.1
George P.*	12	10	2,380	41.0	58.1	2.9	3.9	(1.0)	(4.9)	(−2.0)	0.050	0.067	70	1.2
John H.*	25	24	1,914	43.2	44.3	3.0	3.1	(1.0)	(4.1)	(−1.1)	0.068	0.070	39	1.2
Joseph R.*	16	14	2,493	41.4	60.4	3.3	2.5	(1.0)	(3.5)	(−0.2)	0.055	0.041	54	1.3
		16	2,493	42.0	59.4	3.3	3.9	(1.0)	(4.9)	(−1.6)	0.056	0.066	54	1.3
Hubert W.	14	13	2,312	41.0	56.4	4.3	3.8	2.3	6.1	−1.8	0.076	0.067	70	1.3
Fred B.	18	13	3,277	69.3	47.3	5.0	4.4	1.3	5.7	−0.7	0.106	0.093	59	1.6
John O'C.	15	8	3,422	66.9	51.1	6.0	3.6	0.53	4.2	+1.8	0.117	0.071	47	2.1
Ab. M.	10	7	2,300	65.3	35.2	5.2	9.4	0.8	10.2	−5.0	0.148	0.267	15	1.2
Frank D.	30	26	3,804	82.5	46.1	6.9	3.6	1.8	5.4	+1.5	0.150	0.078	62	2.4
		28	3,574	76.5	46.7	7.2	3.6	1.8	5.4	+1.8	0.154	0.077	56	2.2
George B.	54	9	3,012	52.7	57.1	3.1	4.5	0.9	5.4	−2.3	0.054	0.079	58	1.7

* Cases of McCann and Barr, 1920.

In the first five cases and in the last case shown in Table 7 the nitrogen minimum was attained by reducing the nitrogen intake to a low level (from 2.8 to 4.3 gm. N), at the same time giving a diet, of which the caloric value varied from 1.1 to 1.7 times the basal requirement of the patient. When these six cases are compared with the experiments on normals, which are compiled in Table 8, it will be seen that the urinary nitrogen excretion, in terms of grams per diem, fell to approximately the same level as in most of the normal subjects. A diminution of urinary nitrogen elimination occurred with about the same promptness in both series, following a reduction in food nitrogen. This can best be seen by consulting the graphic figures.

While in grams per diem the urinary nitrogen excretion of the tuberculous patients approaches closely that of normals, when one estimates the amount excreted per kilogram of body weight it is seen to be much higher for the tuberculous series. However, it was not to be expected that the wear and tear quota should vary directly with total body mass. It is rather more probable that it varies with the total metabolism.

In the remaining four cases shown in Table 7 the protein in the diet was only moderately reduced (to the equivalent of 5 or 7 gm. nitrogen daily). The attempt was made rather to determine to what extent the nitrogen excretion could be reduced by the protein sparing action of a diet rich in nonnitrogenous foodstuffs. Positive nitrogen balance was achieved in two of these cases by the ingestion of 6.0 and 6.9 gm. nitrogen, respectively (from 37.5 to 43.1 gm. protein), when the diet furnished from 2.1 to 2.4 times the basal requirement of energy. It will be noted that in the case of George R. (Table 6), that with a diet furnishing 2,932 calories and 43.8 gm. protein an average of 0.67 gm. nitrogen was added to the body daily for a seven day period. Subject Ab. M. showed persistent large losses of nitrogen. It was impossible to give him adequate amounts of food because of digestive disturbances. He had physical signs of a pneumonic consolidation, and it is not known to what extent organisms other than the tubercle bacillus had entered into the production of the pneumonia.

There is evidence that the quality of the protein supplied is an important factor in determining the amount which will cover a given wear and tear quota. Thomas [21] studied the biologic value of various proteins. First, he reached his nitrogen minimum by taking a nitrogen-poor diet. He then found the relative amounts of various proteins

21. Thomas, K.: Ueber die biologische Werthigkeit der Stickstoffsubstancen in Verschiedenen Nährungsmitteln, Arch. f. Physiol, 219, 1909.

required to cover this known wear and tear quota. A few of Thomas' results are given for purposes of illustration. Each 100 gm. of the following proteins will cover the equivalent of the following number of grams of flesh:

Ox-flesh	104.74 gm.
Milk	99.71 gm.
Fish	94.46 gm.
Potato	78.89 gm.
Flour	39.56 gm.
Maize	29.52 gm.

In our three cases in which positive nitrogen balance was obtained with a low protein diet the source of animal protein was chiefly from milk, lean beef, and chicken, with occasionally a little cheese and eggs. In the case of John O'C., 52 per cent. of the protein was from animal sources; with Frank D., 42 per cent.; and with George R., 47 per cent.

In Tables 7 and 8 the percentage of total calories in the form of carbohydrate is given. In the tuberculous series this varies from 15 to 70 per cent., while in the normal series it varies from 38 to 100 per cent. of the total calories. In the case of Ab. M., who showed the greatest nitrogen excretion, only 15 per cent. of the calories were from carbohydrate. In this instance the table may be misleading, for if one refers to Table 2 it is apparent that the nitrogen loss was greater on several days on which a much higher percentage of carbohydrate calories was taken.

There has been a great deal of work done to determine the relative efficiency of carbohydrate and fat as protein sparers. Kayser [22] found that he could not replace carbohydrate in a diet with an isodynamic amount of fat without a rise in the output of nitrogen. Voit and Korkunoff [23] showed that when protein is fed with fat the fall in protein catabolism, although it reaches a level well below that for protein alone, is not so marked as in the case of protein plus carbohydrate. However, Tallquist [24] in Rubner's laboratory found that, keeping the same carbon: nitrogen ratio, the relative proportions of fat and carbohydrate in the diet could undergo considerable variation without disturbing the nitrogen balance greatly. Landergren [25] made a clear demonstration of the difference in sparing action

22. Kayser: Ueber die Eiweisssparende Kraft des Fettes vergleichen mit derjenigen des Kohlenhydrats. DuBois-Reymond Arch. f. Physiol., 371, 1893.

23. Voit, E., and Korkunoff: Ueber die geringste zur Erhaltung des Stickstoffgleichgewichtes noethige Menge von Eiweiss, Ztschr. f. Biol. **32**:58, 1895.

24. Tallquist: Arch. f. Hyg. **41**:177, 1902.

25. Landergren: Ueber die Eiweissumsetzung des Menschen, Skand. Arch. f. Physiol. **14**:112, 1903.

of the two foodstuffs. There was a steady fall in the nitrogen output on an exclusively carbohydrate diet, and when the diet was changed to one exclusively of fat there was a steady and progressive rise. Finally Zeller [26] fed both dogs and men with varying quantities of fat and carbohydrate. He came to the conclusion that from 70 to 90 per cent. of the carbohydrate in a diet could be replaced by an isodynamic amount of fat without the nitrogen minimum, reached by exclusive carbohydrate feeding, being materially affected. The gen-

TABLE 8.—SUMMARY OF NITROGEN MINIMUM EXPERIMENTS ON NORMALS

Author and Subject	Length of Experiment, Days	Day of Experiment	Total Calories in Food	Calories per Kg. Body Weight	Body Weight, Kg.	Food N, Gm.	Urine N, Gm.	Fecal N, Gm.	Total N, Gm.	Nitrogen Balance, Gm.	Food N per Kg., Gm.	Urine N per Kg., Gm.	Per Cent. Calories from Carbohydrate	Reference Number
Hirschfeld														
II 1888	8	6-8	3,462	47.0	73.0	7.46	5.76	1.65	7.41	+0.05	0.102	0.079	..	(13)
Klemperer														
II 1889	8	6-8	5,020	77.0	65.3	5.28	2.51	1.02	3.53	+1.75	0.081	0.038	38	(14)
Sivén 1898	43	42	2,441	42.0	58.9	2.43	1.78	1.33	3.17	−0.74	0.041	0.030	67	(15)
Landergren														
1903 II	4	4	3,374	45.2	73.4	0.82	3.76	0.75	4.51	−3.69	0.011	0.051	95	(16)
III	4	4	3,163	37.8	79.1	2.5	3.95	1.47	5.42	−2.92	0.032	0.050	52	
IV	4	4	2,920	45.0	62.4	2.05	3.04	1.02	4.06	−2.01	0.033	0.049	44	
V	4	4	3,089	38.4	77.3	2.4	4.20	1.33	5.53	−2.13	0.031	0.054	43	
VI	4	4	2,745	36.1	73.4	2.2	4.95	1.28	6.23	−4.03	0.030	0.067	53	
Hindhede (Madsen)		Av.												
VII-15	19	per.	3,796	53.0	71.5	3.62*	3.41	....	....	+0.21	0.051	0.048	61	(17)
Kocher														
R. A. K.	10	5	5,089	64.0	79.2	1.01	2.92	1.16	4.08	−3.07	0.013	0.037	100	
J. G. F.	10	4	5,089	72.0	70.4	1.01	2.89	1.13	4.02	−3.01	0.014	0.041	100	(4)

* Utilizable nitrogen = food N — fecal N.
13. Hirschfeld: Virch. Arch. **114**: 301, 1888.
14. Klemperer: Zeitschr. f. klin. Med. **16**: 550, 1889.
15. Sivén: Skand. Arch. f. Physiol. **10**: 128, 1900.
16. Landergren: Skand. Arch. f. Physiol. **14**: 210, 1903.
17. Hindhede: Skand. Arch. f. Physiol. **30**: 97, 1913.

eral correctness of Zeller's conclusions seems to be borne out by the results in Table 7 and by the experiments of Landergren shown in Table 8.

Attention should next be turned to the observations carried out on Frank D., and George R. during periods of forced feeding. In the case of Frank D. a very striking result was obtained, which was summarized under the case history. The gain of the body in nitrogen was greater on the low protein diets of periods 4 and 5. This was not due to any apparent diminution in the activity of the tuberculous

26. Zeller: Einfluss von Fett und Kohlenhydrat bei Eiweisshunger auf die Stickstoffausscheidung, Arch. f. Physiol. **2**:3, 1914.

process during the latter periods, as evidenced by the physical signs or by the temperature record (Fig. 6). It should be pointed out that the subject was only 17 years old, incompletely developed, and that he had suffered from inanition before coming under observation. However, the periods of high protein feeding preceded the low periods, so that the body had the greater opportunity to store nitrogen first. Recently, von Hoesslin [27] in Germany has studied groups of individuals who were suffering from severe inanition. He noted an abnormally high nitrogen retention during periods of relatively low protein and caloric intake, and that this retention was but little influenced by the caloric value of the food.

In the case of George R., who had been better nourished previously, it was seen that although a slight gain in nitrogen was made when 43.8 gm. protein were ingested, the retained nitrogen increased as the protein ingestion increased. The maximum retention was noted when there was 90 gm. protein in the diet. Less nitrogen was stored when the protein intake was increased to 125 gm. daily.

Extensive and very valuable studies have been made by Bardswell and Goodbody [28] on the effect of large diets on patients with pulmonary tuberculosis. Some of their patients received 270 gm. protein with about 5,000 calories, others more moderate diets with 160 gm. protein and 3,400 calories. The clinical results with the more moderate diet were satisfactory, in fact "the patients made much less satisfactory all-round progress on the very large diets. . . ." Failure of appetite, marked digestive and intestinal derangements were noted. "When the amount of proteid in the diet was much increased, it resulted in an increased excretion of nitrogen out of all proportion to the increased amount retained in the body." The percentage of nitrogen excreted as urea fell. There was an increase in the amounts of aromatic sulphates excreted. Generally the large gains in weight were not permanent, but disappeared on return to a normal diet. Dyspnea was frequently complained of by patients undergoing forced feeding. This we know [2] is the direct result of the effect of the ingestion of food on the respiratory exchange.

In determining, therefore, the optimal quantity of protein for tuberculous patients one must strike a balance somewhere between the two extremes. While some patients can be made to gain nitrogen and weight on diets containing from 37.5 to 45 gm. protein this requires a large allowance of nonprotein food, especially of carbohydrate, in

27. Von Hoesslin, H.: Klinische Eigentümlichkeiten und Ernährung bei schwerer Inanition, Arch. f. Hyg. **88**:147, 1918.

28. Bardswell, Noel, and Chapman, J. E.: In "Diets in Tuberculosis," they give a complete summary of this work, Oxford Press, 1908.

amounts sufficient to bring the total calories up to from 3,500 to 4,000 per diem. When one compares the effect on the pulmonary ventilation produced by the amount of protein, which might be fed at one meal in an ordinary diet (from 30 to 40 gm.), with the effect of the amount of carbohydrate to be fed at one meal with a forced diet, the effect of the ordinary amount of protein becomes insignificant. Our results have shown that nitrogen balance may be established at from 10 to 15 gm. nitrogen (62 to 93 gm. protein), with a rather moderate number of

TABLE 9.—SUMMARY OF NITROGEN MINIMUM EXPERIMENTS IN VARIOUS DISEASES

Author; Subject; Disease	Length of Experiment, Days	Day of Experiment	Total Calories in Food	Calories per Kg. Body Weight	Body Weight, Kg.	Food N, Gm.	Urine N, Gm.	Fecal N, Gm.	Total N, Gm.	Nitrogen Balance, Gm.	Fecal N per Kg., Gm.	Urine N per Kg., Gm.	Reference Number
Psoriasis *													
8 VI.....	7	..	1,866	32.0	58.4	4.39	1.88	1.97	3.85	+0.54	0.075	0.032	(18)
9 III.....	7	..	1,555	28.5	54.6	4.29	2.99	1.93	4.92	—0.63	0.079	°0.055	
9 IV.....	7	..	1,666	....	54.5	5.16	2.47	1.89	4.36	+0.80	0.095	0.045	
Kocher													(4)
Paratyphoid													
T., 38.5 C.	16	7	3,213	56.0	....	2.2	14.52	0.88	15.40	—13.2	0.035	0.230	
T., 38.1 C.	16	10	4,666	78.0	....	3.5	5.82	0.88	6.70	—3.2	0.056	0.097	
T., normal.....	16	16	4,666	78.0	....	3.5	4.79	0.76	5.55	—2.05	0.056	0.080	
Erysipelas													
J. S., T.,39.5 C.	10	4	4,255	74.5	55.8	1.82	13.34	1.08	14.37	—12.55	0.033	0.240	
J. S., T., 38 C. ..	10	9	4,280	75.0	53.8	1.88	11.52	1.08	13.55	—11.67	0.035	0.210	
E. M., T., 39.6 C.	6	6	3,360	73.0	46.0	2.02	16.02	....	.....	.....	0 044	0.350	
R. M., T., 39-40 C.	6	2	4,050	....	61.0	2.01	9.35	0.94	10.29	—8.28	0.033	0.156	
R. M., T.,normal	..	6	4,230	....	60.0	1.05	4.04	0.94	4.98	—3.93	0.018	0.067	
Lobar pneumonia.....	8	8	3,960	63.0	62.9	1.84	13.40	1.20	14.60	—12.76	0.029	0.213	
Acute polyarthritis													
E. S., T., 40 C. ..	11	7	2,600	....	33.5	1.12	11.48	0.92	12.40	—11.28	0.033	0.342	
E. S., T, normal	..	11	2,840	....	33.5	1.12	3.52	0.92	4.44	—3.32	0.033	0.105	
Basedow's disease													
J. A. D.	16	14	2,480	....	50.7	3.13	3.19	1.15	4.34	—1.21	0.062	0.063	(19)
Syphilis, secondary—IIIa.....	8	5	2,408	43.0	56.0	1.6	3.6	0.9	4.5	—2.9	0.029	0.064	(20)

18. Schamberg, Kolmer, Ringer and Raiziss: Jour. Cut. Dis., Oct., Nov., 1913.
19. Rudinger: Wein. klin. Wchnschr. **21**: 1581, 1908.
20. Cederkreutz, A.: Beitrage zur Kenntnis des Stickstoffwechsels in der Frühperiode der Syphilis, Breslau, 1902.

calories in the diet (2,500). We have no evidence of any advantage of ingesting an excess over 90 gm. protein. If a maximum of 90 gm. per diem were given the stimulating effect of the protein taken at any one meal would be negligible. It should be possible to give most patients at least 150 gm. fat, which would require only 150 gm. carbohydrate to bring the total energy value up to 2,500 calories. Such a diet could be taken at the least expense of respiratory function.

SUMMARY AND CONCLUSIONS

1. In nine of the ten tuberculous patients studied the minimal urinary nitrogen excretion observed was between 2.5 and 4.5 gm. per diem, and between 0.041 and 0.093 gm. per kilogram per diem. In one case the lowest excretion of urinary nitrogen was 9.4 gm. per diem, or 0.267 gm. per kilogram. In the nine cases with a minimal nitrogen excretion the diet given had an energy value from 1.1 to 2.4 times the basal energy requirements of the subjects, and furnished 39 to 70 per cent. of the calories in the form of carbohydrate.

2. In some cases it is possible to maintain nitrogen balance, and even to retain nitrogen, when from 37 to 44 gm. protein are ingested, of which about one half is from animal sources. The attainment of nitrogen equilibrium with such a small amount of protein is dependent upon the ingestion of large amounts of carbohydrate and fat, sufficient to make the total caloric value of the diet from 1.7 to 2.4 times the basal energy requirement.

It is probable that the failure to establish nitrogen balance on such low protein diets is due to failure or inability of the subject to ingest sufficiently large quantities of carbohydrate and fat, rather than that it is due to an inherently large wear and tear quota in tuberculosis.

3. Positive nitrogen balance in bed patients may be attained by the ingestion of from 60 to 90 gm. protein when the diet contains carbohydrate and fat, with a total caloric value of less than 1.7 times the basal requirement. The evidence indicates that the optimal quantity of protein for patients who are confined to bed with pulmonary tuberculosis, lies between the limits of 60 to 90 gm. per diem, when the caloric value of the diet is about 2,500 calories. Additional carbohydrate and fat calories must be furnished when patients are allowed to exercise.

OBSERVATIONS ON THE USE OF QUINIDIN IN AURICULAR FIBRILLATION *

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A great deal of interest has been aroused by the recent reports on the favorable action of quinidin in auricular fibrillation. Since Frey's [1] first publication in 1918, the results from the treatment of over one hundred cases have appeared, nearly half of which have been reported by Frey.[2] The literature is given in the recent article by Levy,[3] who also reports the results on four cases. The purpose of this report is to record the experience in the use of this drug in two cases selected from a number under observation in this clinic. The first of these cases is reported to bring out a point which in our opinion has not been emphasized sufficiently, namely, the danger in the use of this drug in certain cases. The other case illustrates the strikingly favorable action of quinidin in the rather rare condition in which auricular fibrillation is uncomplicated by advanced valvular or myocardial damage and in which no serious break in compensation has occurred.

ABSTRACT OF CASE REPORTS

CASE 1.—Mrs. P. F. S., aged 47, white, admitted to hospital, April 5, 1921, complaining of shortness of breath and palpitation. From the history, it was evident that from moderate to severe cardiac decompensation with irregular pulse had been present for the preceding seven months. Previous to this time there had been no serious decompensation. The diagnosis was chronic endocarditis, mitral incompetence, cardiac decompensation, auricular fibrillation. Examination revealed cyanosis, dyspnea, hydrothorax, ascites and edema of the extremities. On admission the ventricular rate was 124; radial rate, 110. Venous pressure was 23 cm. of water. Urine output in the first twenty-four hours was 7 ounces. As a result of rest and treatment all symptoms improved. the ventricular rate and pulse deficit decreased, the venous pressure fell and urine output increased.

April 19, the apical rate was 80; radial, 76; venous pressure, 8 cm. Urine output was 36 ounces. Cardiac area as determined by the teleroentgenogram showed definite reduction over that present on admission. The condition continued to improve, and by May 7, ascites, hydrothorax and nearly all trace of peripheral edema had disappeared. The patient was up in a chair for several hours daily and was allowed moderate exercise. Auricular fibrillation persisted, however, and numerous electrocardiograms taken during residence in the hospital failed to reveal a normal cardiac rhythm at any time.

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* From the Bradley Memorial Hospital, Department of Clinical Medicine of the University of Wisconsin.

1. Frey, W.: Ueber Vorhofflimmern beim Menschen und seine Beseitungung durch Chinidin, Berl. klin. Wchnschr. **55**:417, 1918.

2. Frey, W.: Chinidin zur Bekämpfung der absoluten Herzunregelmässigkeit, Deutsch. Arch. f. klin. Med. **136**:70, 1921.

3. Levy, R. L.: Restoration of the Normal Cardiac Mechanism in Auricular Fibrillation by Quinidin, Arch. Int. Med. **76**:1289 (May 7) 1921.

May 17, quinidin sulphate was given in doses of 0.25 gm. every fourth hour for four doses. After three doses (0.75 gm.) auricular tachycardia developed with a rate of 180. After an hour or so, periods of auricular fibrillation alternated with the periods of rapid regular heart action. Palpitation, dyspnea and cyanosis developed. Venous pressure rose to 12 cm. Urine fell to 26 ounces. During the night, a few hours after the last dose of quinidin, heart action became more stable. On the following morning, quinidin administration was begun again with the same dosage as on the previous day. Palpitation, cyanosis and dyspnea again appeared. The urine was 21 ounces, the venous pressure 11 cm. Electrocardiograms showed periods of tachycardia interspersed with periods of auricular fibrillation. The symptoms again subsided with the cessation of quinidin administration the following night. The following morning (May 19) quinidin administration with the same dosage was begun again. A short time after the first dose, extreme distress developed. There was dyspnea (respiratory rate 36), marked cyanosis, palpitation, pain in side and cough with expectoration of blood streaked sputum. Examination revealed right sided hydrothorax, pulmonary edema, ascites, tympanites, and slight edema of the extremities. Venous pressure rose to 18 cm. Electrocardiograms revealed the same type of rhythm as on the two previous days. The cardiac area was increased (teleroentgenogram). Due to the critical condition of the patient and the absence of any favorable action on the cardiac rhythm, quinidin administration was stopped after the third dose on this day, and digitalization with general treatment for cardiac decompensation established. A total of 2.75 gm. quinidin sulphate had been administered. On the following two days the condition was critical. The venous pressure had risen to 21 cm., the urine had fallen to 6 ounces in twenty-four hours. Continuous auricular fibrillation persisted with an average apical rate of 136 and radial of 82. By the next day (May 22) the general condition had begun to improve. Venous pressure had fallen to 16 cm. and urine increased to 16 ounces. Steady improvement continued and June 3, the patient was discharged from the hospital free from any symptoms or signs of decompensation. Auricular fibrillation, however, was still present, with an apical rate of 72 and with a very small pulse deficit. On discharge the venous pressure averaged 7 cm. and the urine was approximately equal to the fluid intake.

Case 2.—L. J. R., white, male, university student, aged 23, came under observation for the first time Aug. 7, 1919, complaining of shortness of breath, palpitation and irregular heart action. This condition developed on the third day of a rather severe influenzal attack in November, 1918. No heart irregularity or palpitation was noted previous to this time. Following recovery from the attack of influenza, the cardiac irregularity persisted. Shortness of breath was present on very slight exertion and at times paroxysms of dyspnea with severe cardiac palpitation occurred, even when the patient was at rest. Examination revealed marked irregularity of the heart with considerable pulse deficiency. There was, however, no evidence of venous stasis in lungs, liver or other organs, and no adventitious heart sounds were heard. The cardiac area (roentgenogram) was increased approximately 25 per cent. The enlargement was symmetrical. Electrocardiograms revealed auricular fibrillation. The past medical history was unimportant and furnished no evidence of cardiac involvement previous to the attack of influenza.

Under restricted activity and dietetic control, the condition improved somewhat. The patient was again examined Jan. 29, 1920. General health had been fair for the past few months, and he had been able to pursue his university work on a restricted schedule. There had been no symptoms of severe cardiac incompetence. Moderate exercise could be taken without extreme shortness of breath. Examination revealed a cardiac area somewhat smaller than previously observed (approximately 20 per cent. above normal), totally irregular cardiac rhythm, no adventitious sounds and no evidence of venous stasis.

The patient entered the hospital June 28, 1921, for treatment with quinidin. The irregular heart action had persisted without apparent interruption from its initiation thirty-one months previously. For the past year he has had to give up practically all work, due to frequent periods of shortness of breath and general weakness. Rather severe attacks of palpitation and dyspnea, lasting from fifteen to twenty minutes, have occurred every few days and have increased in frequency recently. There has been, however, no serious cardiac incompetence at any time. For the past eighteen months he has had abdominal symptoms which were stated by the physician in attendance to be due to spastic colitis.

Examination revealed practically the same condition as found at the two previous examinations, thirty-one and eighteen months ago. The cardiac area was found to be less than 15 per cent. above normal. No adventitious heart sounds were heard. The patient was kept at rest in bed for five days without medication. Repeated electrocardiograms were made during this time, all showing uninterrupted auricular fibrillation. The apical rate averaged 115, the radial 94. Venous pressure varied between 8 and 9 cm. of water in the dorsal prone position. Urine output was normal.

July 4, the patient was given a single dose of 0.25 gm. quinidin sulphate by mouth. About two hours later an electrocardiogram revealed periods of tachycardia interspersed with periods of fibrillation. On the next day (July 5), he was given 4 doses of 0.25 gm. quinidin at three hour intervals. There developed brief periods of rapid regular heart action with moderate distress (palpitation and shortness of breath). No other signs of circulatory deficiency were present. The apical rate averaged 120, the radial 110. Venous pressure was unchanged. Urine output was normal.

July 6, six doses of 0.25 gm. quinidin at two hour intervals were ordered. Before the first dose, rather frequent series of rapid regular beats were present, interspersed with periods of fibrillation. At 4 p. m., following the fourth dose of quinidin, the patient became uncomfortable, due to palpitation and shortness of breath. The pulse became exceedingly irregular in force and rhythm. Electrocardiograms made at this time showed continuous fibrillation with a ventricular rate of 120. The subjective distress increased somewhat until about 6 p. m., when the patient fell asleep. On awakening in about half an hour, all distress had disappeared and cardiac action was found to be entirely regular in force and rhythm. Electrocardiograms revealed a normal sino-auricular rhythm with a rate of 66, with normal P-R interval and without evidence of preponderance of either ventricle.

The patient was discharged from the hospital July 14. Subsequent to its initiation, eight days previously, normal heart action had persisted without interruption. For the first two days following the return of normal rhythm, a single dose of 0.25 gm. quinidin sulphate was given daily, subsequently a single dose every other day, to be continued after leaving the hospital. All symptoms disappeared and examination failed to reveal any abnormality with the exception of slight symmetrical cardiac hypertrophy (15 per cent.). The pulse rate averaged approximately 60 during this period. The venous pressure (dorsal prone position) fell to 5 cm. shortly after the establishment of normal cardiac rhythm and remained at this point.

COMMENT

No one who has carefully followed the action of quinidin on the heart in auricular fibrillation can be but impressed with the powerful action of this drug on the cardiac mechanism in this condition. Clinical experience has shown that its action is sufficient to restore the normal mechanism at least temporarily, in approximately half of the cases of auricular fibrillation in man. Much of this experience is too recent,

however, to state in how large a percentage permanent success can be obtained. Since in most cases conditions tending to produce auricular fibrillation are probably still present even after the normal rhythm is restored, subsequent administration of the drug may be necessary to avoid recurrence. Additional experience will be necessary before the details of this will be clear. In most cases, perhaps in all, disturbances of rhythm occur during the transition stage between auricular fibrillation and sino-auricular rhythm. The most characteristic and frequent of these transition rhythms is rapid regular heart action (auricular tachycardia, "auricular flutter") occurring either alone or in periods interspersed with periods of fibrillation. These intermediary stages may occur even when the normal rhythm is not subsequently restored, as in the first case presented here. It is apparently the result of these stages of transition in which the dangers of the treatment lie. While acutely developing auricular fibrillation undoubtedly causes considerable mechanical deficiency of the heart (Eyster and Swarthout [4]) and is probably not infrequently the immediate cause of cardiac decompensation, the heart may compensate for this as it does for valve injury, particularly when it is assisted by the protective influence on ventricular stimulation of digitalization. That the removal of this compensated auricular fibrillation under the action of quinidin in producing transition rhythm may destroy clinical cardiac compensation, is illustrated by the first case reported. Possibly also the contractility of the ventricular muscle is reduced by the drug. The case again becomes critically ill, and if restoration of the normal sino-auricular rhythm fails, as it apparently so frequently does in the older and more severe forms of chronic heart disease, the best that can be hoped for is a tedious restoration of compensation with another period of cardiac failure with its attendant permanent damage to be charged to the quinidin treatment. On the other hand, when auricular fibrillation is unassociated with valvular or severe myocardial damage and with no history of severe circulatory failure, the cardiac reserve is able to carry the circulation through the periods of "transition rhythm" with only transitory circulatory deficiency.

With a therapeutic agent as definite in its action as quinidin of use in a clinical condition as common and important as auricular fibrillation, it is inevitable that great interest in and widespread use of the remedy will follow. We have attempted to point out a definite danger in its use and the necessity of the utmost care in its administration to at least the more severe forms of chronic heart disease. In such cases it should be used only, first (as has been pointed out by Frey) after compensa-

4. Eyster, J. A. E., and Swarthout, E.: Experimental Determination of the Influence of Abnormal Cardiac Rhythms on the Mechanical Efficiency of the Heart, Arch. Int. Med. **25**:317 (March) 1920.

tion is as thoroughly established as possible; and second, only when the patient can be under almost continuous observation, when frequent electrocardiograms are obtained, and when repeated physical examinations are made for signs of breaking compensation. For the present, and until more experience is gained as to the mode of action, contraindications, the size of dose and the frequency of administration for the best results, the treatment of the more severe cases should be carried out only in a hospital under strict regulation and observation. The patient should be prepared for a break in compensation by rest in bed and limitation of food and liquids during the period of administration.

TUBERCULOSIS OF THE HEART

WITH THE REPORT OF TWO CASES *

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In a study of 7,219 necropsies Norris [1] found 1,780 tuberculous cases and among these eighty-two cases of tuberculous pericarditis. In five cases the heart muscle was involved. This indicates the relative infrequency of the conditions being reported. A point of added interest is the unusual degree of involvement in the first case.

REPORT OF CASES

CASE 1.—*History.*—The patient, a colored male, aged 25, was admitted to the Jefferson Hospital, on the service of Dr. H. A. Hare, Dec. 27, 1920, complaining of pain in the upper half of the abdomen and chest. His family history was negative for tuberculosis. He had gonorrhea in 1909 and syphilis in 1913, for which he received no treatment. In October, 1918, he had an attack of influenza and since then a persistent cough at night. In July, 1920, he developed abdominal pain which grew progressively worse and about December, 1920, his abdomen began to enlarge. His cough became more severe; he was dyspneic and complained of pain in his chest. He stated that he had lost 40 pounds in the past year.

Examination.—On examination there were evidences of a pleural effusion at the right base and immense enlargement of the heart—both confirmed by roentgen ray. His abdomen was slightly distended and tender and the liver could be palpated at the level of the umbilicus in the right midclavicular line. There was some fluid in the left tunica vaginalis. Blood count showed a leukopenia and moderate secondary anemia; his blood Wassermann was positive; his sputum was negative for tubercle bacilli. He died Feb. 21, 1921, and necropsy was performed the same day.

Necropsy Report.—The body was that of an adult colored male, weighing about 170 pounds. The heart and pericardium were immensely enlarged, weighing 1,580 gm., the pericardial cavity being obliterated by large, dense, yellowish nodules which invaded the heart muscle, auricles and ventricles to a similar degree. The nodules were continuous with the mediastinal and peribronchial lymph nodes which were also large, yellowish and firm. No tuberculosis of the lungs could be established but the pleurae averaged about 0.4 cm. in thickness and this thickening was especially marked at the right base which contained an encapsulated effusion of about 700 c.c. of brownish-red serum. The spleen, right suprarenal, kidneys and liver showed a number of firm, yellowish nodules scattered throughout. At the juncture of the ileum and cecum was a large ulcer, 2.5 cm. in diameter, with base of reddish granulations and firm, undermined edges. This, with the large, firm and yellowish mesenteric and retroperitoneal nodes aided in the gross diagnosis of tuberculosis.

The microscopic study revealed a fibrocaseous tuberculosis of the following organs and tissues: pericardium and myocardium, pleurae, spleen, right adrenal, kidneys, liver, mediastinal, mesenteric and retroperitoneal lymph nodes.

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* Read before the Pathological Section of the National Tuberculosis Association, New York City, June 16, 1921.

* From the Department of Pathology, Jefferson Medical College.

1. Norris, G. W.: Tuberculous Pericarditis Based on a Study of 7,219 Autopsies in Philadelphia Hospitals, Univ. Penn. M. Bull. **17**:155, 1904.

No typical tubercles were seen and very few giant cells. Smears from the fresh material and stained sections of pericardium, pleura and retroperitoneal nodes were studied for tubercle bacilli but failed to reveal the organism. Guinea-pig inoculation, however, produced a diffuse tuberculous lymphadenitis and tuberculosis of the spleen. Smears from the caseous nodes showed many tubercle bacilli but attempts to culture the organism failed.

CASE 2.—S. W., a colored male, aged 25, dishwasher by occupation, was admitted to the Department for Diseases of the Chest of the Jefferson Hospital, March 15, 1921.[2] He complained of a dull pain in the back and sternal region and of a moderate cough productive of a large amount of mucoid sputum which was occasionally blood-streaked.

Family History.—Negative for tuberculosis.

Fig. 1.—Case 1. Tuberculous pericarditis and myocarditis. Note the invasion of heart muscle by the immense, tuberculous nodules of the pericardium, shown best by insert in left hand corner.

Personal History.—He had a chancre in 1913 and gonorrhea in 1914. He stated that he had been in poor health ever since his discharge from the army in 1918. At that time he noticed a cough. Shortly after the onset he became short of breath on slight exertion and felt weak. From time to time he had a vague pain in the front of the chest. Increasing disability caused him to give up his work in the latter part of January, 1921. He entered a Philadelphia hospital and was later transferred to the Jefferson Chest Hospital.

2. I am indebted to Dr. E. H. Funk for the clinical notes of this case.

Physical Examination.—This showed an emaciated, colored, adult male. His pupils reacted normally. Throat was red, tonsils swollen. The cervical lymph nodes were distinctly palpable with a small mass of enlarged glands above the clavicle on the left side. Chest was long, narrow and flat. Expansion was generally limited. Vocal fremitus was increased throughout the right side of the chest and the percussion note was generally impaired. Breath sounds were distinctly audible with a blowing characteristic over the entire chest except the right base posteriorly where the intensity was diminished. Many squeaking sounds were heard with numerous crackling râles throughout, especially

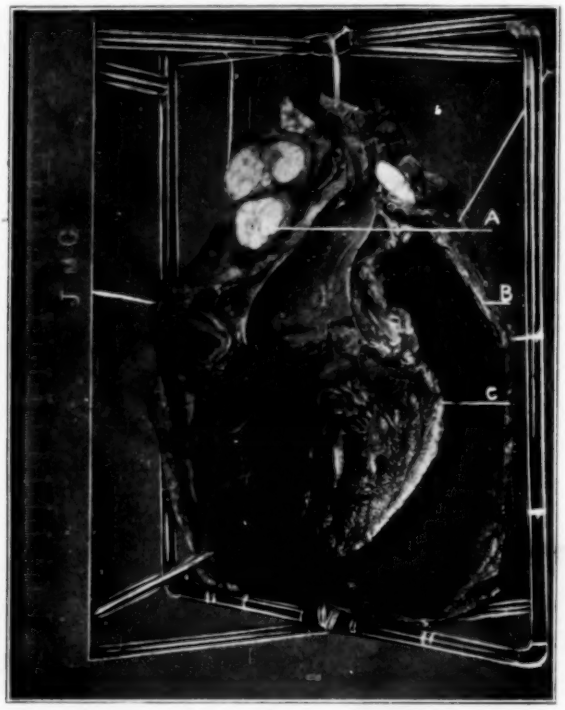

Fig. 2.—Case 2. Tuberculous pericarditis, showing (a) enlarged, tuberculous nodes at the base of the heart; (b) thickened, parietal pericardium, and (c) tuberculous nodules of visceral pericardium.

on the right side. Whispering pectoriloquy was noted in the third interspace on the right side, anteriorly.

Heart: There was marked precordial pulsation with an increase to the left in the lateral diameter of cardiac dulness. Heart action was rapid but regular; heart sounds were distinctly heard; no murmurs were present. Sputum examinations were repeatedly negative for tubercle bacilli. Urine contained a trace of albumin and an occasional hyaline cast. Temperature, 102 F.; pulse, 130; respirations, 40. Patient died, April 25, 1921, and a necropsy was made the following day.

Necropsy Report.—The important findings were as follows: The anterior cervical lymph nodes were distinctly palpable and those on the left side just above the clavicle were especially enlarged. There were several enlarged, firm, yellowish nodes adherent to the posterior surface of the sternum. All of the mediastinal nodes were similarly enlarged, clustered about and pressing on the trachea and larger bronchi. These nodes varied in size from less than 1 cm. to 3 or 4 cm. in diameter. Some had caseous centers.

The pericardial cavity was distended with about 700 c.c. of blood-tinged serous fluid. There was likewise a dense, yellowish, fibrinous exudate present.

Fig. 3.—Case 2. Tuberculosis of peribronchial lymph nodes with practically no lung involvement.

The visceral pericardium of the left ventricle was distinctly thickened, measuring about 0.3 cm., and consisted of a zone of dense, yellowish tissue made up of conglomerate nodules which grew larger near the base of the ventricle at the reflection of the pericardium. These nodules, unlike those of the first case, showed no tendency to invade the heart muscle. The lymph nodes at the base of the heart were of the same type as the mediastinal nodes and were continuous with them, pressing on the great vessels. These nodes were likewise firmly adherent to the pericardium.

Left Lung: The left pleural cavity contained about 500 c.c. blood-tinged serous fluid and the lung was compressed. On section the pulmonary tissue was dark red in color and only partially crepitant. About 6 cm. from the apex, on the anterolateral surface of the lung, was a conglomerate caseous tubercle, a little less than a centimeter in diameter. There was no further evidence of tuberculosis in the lung structure; the nodes at the hilus, however, were greatly enlarged, similar to and continuous with the mediastinal nodes.

Right Lung: It was more voluminous than the left but on section presented nearly the same appearance. Near the hilus, a little area of pulmonary tissue, about 2 cm. in diameter, adjacent to an enlarged and caseous lymph node, showed tuberculous infiltration.

None of the other organs showed any evidence of tuberculosis but the mesenteric and retroperitoneal lymph nodes were moderately enlarged, firm and yellowish.

A few tubercle bacilli were found in smears from the caseous mediastinal nodes.

Microscopic study revealed a typical caseous tuberculosis of the structures mentioned. The pericardium showed the lesion especially well; unlike the first case, there were many typical tubercles present with caseous centers and numerous giant cells. The tuberculous process, as mentioned in the gross description, exhibited no tendency to invade the myocardium.

Guinea-pigs were inoculated with emulsified caseous nodules from the base of the heart. The animals, killed six weeks later, showed tuberculosis of the abdominal lymph nodes and spleen. A number of tubercle bacilli were recovered in smears but cultures both on Petroff's and Dorset's mediums failed to develop the organism.

COMMENT

In 1902 Anders[3] summarized seventy-one cases of tuberculosis of the myocardium and added a case of his own. He classified the condition as occurring in three forms: (1) large tubercles; (2) miliary tubercles (less common) and (3) diffuse form or tuberculous infiltratiton (rare). He stated that cardiac tuberculosis was most frequent in early life, 40 per cent. of his cases occurring under 15 years. In a large proportion of cases, the lungs and bronchial glands were tuberculous. In twenty-nine out of thirty-one cases in which the glandular condition was noted, tuberculosis was present and this he believed to be the seat of the disease. This extended from the bronchial to the mediastinal nodes and thence directly to the heart or quite commonly by way of the pericardium.

Cases very similar to the present ones have been reported by Ellis,[4] Raviart and Caudron,[5] Benda and Geissler,[6] Toldt,[7] Passamonti,[8]

3. Anders, J. M.: Tuberculosis of the Myocardium, J. A. M. A. **39**:1081 (Nov. 1) 1902.

4. Ellis, A. G.: Heart Showing Chronic Tuberculosis of the Pericardium, with Involvement of the Myocardium, Proc. Path. Soc., Phila., June, 1903.

5. Raviart and Caudron: A Case of Tuberculosis of the Myocardium, Echo méd. du Nord **8**:529, 1904.

6. Benda, C., and Geissler: New Cases of Tuberculosis of the Heart and Blood Vessels, Deutsch. med. Wchnschr. **31**:1169 (July 20) 1905.

7. Toldt, G.: A Case of Tuberculosis of the Myocardium, Rev de méd. **26**:101, 1906.

8. Passamonti, M.: A Case of Tuberculosis of the Myocardium, Policlinico, Rome **14**:88, 1907.

Beifeld,[9] Fraga,[10] and more recently by Adamson,[11] Doermer,[12] and Binder.[13]

Ellis' case presented, in addition to tuberculous pericarditis and myocarditis, tuberculosis of the mediastinal nodes and lungs and a miliary tuberculosis of liver, spleen, pancreas and kidneys. Only after a study of many blocks from the heart were a few tubercle bacilli seen in one section. Beifeld's case showed a tuberculous scar at the apex of the left lung and a caseous tuberculosis of the mediastinal, tracheal, bronchial and left lower cervical nodes. There was a tuberculous pericarditis with total obliteration of the pericardial sac. The liver and spleen contained conglomerate tubercles. Microscopic examination demonstrated typical tuberculous tissue but up to the time of his report search for tubercle bacilli in the tissues was unsuccessful. He concluded that infection traveled from the left apex to the mediastinal nodes and then by contiguity or lymphatic extension or both, to the pericardium and by contact infection to the heart muscle. In Adamson's case no evidence of tuberculosis was found in the lungs or bronchial lymph nodes but he felt that the process probably started in the nodes at the base of the heart.

It is generally conceded that the mediastinal nodes act as the focus of infection for the pericardium and myocardium in this condition. Toldt however, reports a case of tuberculosis of the heart (limited to the right auricle) with no sign of pericardial involvement. He found but little evidence of tuberculosis disease in the tracheobronchial nodes but did note a healed lesion at the apices of both lungs. In commenting on the condition he mentions that Fuchs in a report of fifty-three cases of tuberculosis of the myocardium, found twelve cases of isolated auricular tuberculosis. Of these the right auricle alone was affected in nine; both auricles in two; and the left auricle only in one. Of the twelve cases eight showed tuberculous pericarditis, in two the pericardium was unaffected and in two the condition was not stated.

Passamonti also reports a case of tuberculosis of the myocardium with no other tuberculous lesion except a nodule in the lower lobe of the left lung. He did not feel that the usual propagation of infection (glandular) had occurred in his case. In a discussion of the condition

9. Beifeld, A. F.: Tuberculosis of the Myocardium, with the Report of a Case, Tr. Chicago Path. Soc. **8**:104, 1909-1912.

10. Fraga, C.: Concerning a Case of Cardio-Tuberculous Cirrhosis, Brazil-med. **31**:398, 1917.

11. Adamson, W. W.: A Case of Tuberculosis of the Myocardium. J. Path. & Bacteriol. **23**:399 (Dec.) 1920.

12. Doermer, W.: A Case of Conglomerate Tuberculosis of the heart, Diss., Jena, 1918.

13. Binder, A.: Tumor-Like Tuberculosis of the Heart, Zentralbl. f. inn. Med. **41**:462, 1920.

he mentions that the finding is practically always a postmortem one, and from a study of the literature brings out the fact that there are no characteristic signs of tuberculosis of the heart. He states that attacks of dyspnea, cyanosis, arrhythmia and enlargement of the cardiac area have been observed but adds that hypertrophy and dilatation are not always noted. Raviart and Caudron record a case in a white male, aged 31, with vague symptoms of oppression and pain in the epigastrium, and no definite physical signs. Necropsy revealed a tracheobronchial glandular tuberculosis and tuberculosis of the heart (confined to the right auricle). Toldt's case, mentioned above, occurred in a woman of 58 who had been ill for eighteen months, but, with "no symptoms of localization." Examination showed deviation of the apex of the heart, arrhythmia and muffled apical meurmurs—no other physical signs.

Anders made note of the following symptoms: palpitation, feeble heart sounds, pericardial distress, diffuse pulsation, tumultuous and rapid heart action, fetal and gallop rhythym, rarely murmurs, sudden and recurring syncope, dyspnea, cyanosis, unconsciousness, general edema and sudden death. But he states, "in all this list there is nothing specific, no single symptom or combination of symptoms that is not seen in functional and organic disease of the heart other than tuberculosis. Often the patient dies without a symptom that would attract special attention to the heart." Eisenmeyer is quoted by Anders as stating that a diagnosis may occasionally be made by the presence in a victim of general tuberculosis of sudden, severe collapse, quickly passing; and the detection of weak endocardial murmurs varying in phase and intensity.

One point not mentioned in the cases cited, is the apparently, relatively frequent occurrence of this unusual form of tuberculosis in the colored race. Four cases, Ellis', Beifeld's and the two making up the present report, occurred in young, adult, colored males. For this reason it seems reasonable to suggest that when evidence of cervical and mediastinal glandular disease exists in a young colored man with indefinite symptoms referable to the circulatory system and possibly signs of cardiac enlargement—tuberculosis of the heart should certainly be considered. In this connection Biefeld's case merits particular mention. A colored male, aged 21, had dyspnea and cyanosis; cough; rapid, regular pulse of good quality; and an evening rise of temperature. Examination showed a heart enlarged to right and left. No murmurs were present but a systolic retraction was noted, in place of the apex beat. A clinical diagnosis was made of adherent pericardium, tuberculous in nature; the necropsy, as above described, confirmed this diagnosis.

SUMMARY

The brief clinical reports and necropsy findings of two colored, young, adult males are recorded. Symptoms and physical signs were vague; necropsy demonstrated an immense, fibrocaseous tuberculous involvement of the lymph nodes of the thorax, with extension to the pericardium and in the one case to the heart muscle, causing tremendous enlargement of the organ. Reference to the literature indicates that the heart involvement is almost always secondary to the disease of the mediastinal lymph nodes. The practical limitation of the process to the lymph nodes, the curious reaction of the tissues and the difficulties in the diagnosis of such conditions are some of the problems offered to pathologist and clinician by these case reports.

I am indebted to Dr. H. A. Hare and Dr. Thomas McCrae for permission to report these cases.

OBSERVATIONS FOLLOWING INTRAVENOUS INJECTIONS OF HYPERTONIC SALT SOLUTIONS IN CASES OF NEUROSYPHILIS *

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INTRODUCTORY

Weed and McKibben [1] and others [2] have shown that the administration of hypertonic salt solutions in the cat causes a marked and prolonged fall in cerebrospinal fluid pressure. By an ingenious method they were further able to show that with this fall in pressure a considerable amount of subarachnoid fluid was dislocated into the nervous system; that the fluid "passed along the perivasculars into the substance of the nervous system, reaching the interfibrous spaces in the white matter and the pericellular spaces in the gray." The method leading to these conclusions consisted in allowing a few cubic centimeters of iron-ammonium citrate and sodium ferrocyanid to run into the subarachnoid space as the cerebrospinal fluid pressure (after intravenous injection of hypertonic salt solution) reached zero or was rapidly falling; then fixation of the central nervous system in liquor formaldehyd acidified with 5 per cent. hydrochloric acid precipitated Prussian blue (readily demonstrable microscopically) at points to which the injected citrate and ferrocyanid had penetrated. Foley and Putnam [2] later showed that similar falls in cerebrospinal fluid pressure (presumably with the same dislocation of fluid) could be obtained in cats by administering approximately similar doses of salt per duodenum or per rectum.

In view of these observations, Foley raised the question as to whether or not intraspinal injections of arsphenamized serum in man might be more effectively distributed if followed by the administration of salt either by mouth, rectum or vein. In patients there is no way of determining how extensive the distribution of intraspinal injections actually is. Effective distribution can only be inferred from favorable clinical and serologic results. In the cat, when cerebrospinal fluid pressure (after intravenous injection of salt solution) is reduced to zero or to a negative figure, an intraspinally injected substance can be

* From the Medical Service of the Peter Bent Brigham Hospital.

1. Weed and McKibben: Pressure Changes in the Cerebrospinal Fluid Following Intravenous Injections of Solutions of Various Concentrations, Am. J. Physiol. **48**:512 (May) 1919.

2. Foley and Putnam: Effect of Salt Ingestion on Cerebrospinal Fluid Pressure and Brain Volume, Am. J. Physiol. **53**:464 (Oct.) 1920.

shown to be dislocated into the substance of the nervous system. Consequently, in man it would seem reasonable to suppose that the fluid content of the subarachnoid space passes similarly into the brain substance after intravenous salt injections, if cerebrospinal fluid pressure falls in man as in cats. Such a displacement of injected serum would seem especially to be desired in cases of neurosyphilis with few or no posterior root symptoms, i.e. those cases[3] with cerebrospinal fluids showing pleocytosis, increased globulin and strongly positive Wassermann reaction, but with purely subjective evidences of disturbance and with reflexes for the most part intact.

The first problems were to determine the optimum salt dosage and means of administration, and to ascertain whether intravenous injection of hypertonic salt solutions cause a fall in cerebrospinal fluid pressure in man as in the cat. Foley and Morris, attempting alimentary administration of salt in several preliminary observations, were soon convinced of its impracticability; almost without exception doses of from 15 to 30 gm. (in capsules) were promptly rejected, whether given orally or rectally. Intravenous solutions of varying hypertonicity were later tried by me and 15 per cent. solutions were finally adopted as the optimum. It was soon found that patients could tolerate in this concentration with no very alarming symptoms 410 mg. salt per kg. of body weight. Slight variations in dosage above and below this figure produced such negligible change in effect that it was eventually decided to use as a routine salt dosage 200 c. c. of a 15 per cent. solution.

With the assistance of several cooperative patients it was possible to get actual graphic records in man of the changes in cerebrospinal fluid pressure during and for about thirty minutes after the intravenous injection of the routine salt solution. The procedure was as follows: Lumbar puncture was performed with a small bore needle (patient in the usual position on the right side) and a glass capillary manometer containing normal salt solution was attached, with the loss of as little cerebrospinal fluid as possible, usually only a drop or two. Five or ten minutes were allowed to elapse until a reliable normal could be read; no readings were taken unless cardiac and respiratory fluctuations in pressure evidenced the technical integrity of the apparatus. The intravenous salt solution was then given through a No. 19 needle by gravity, the patient having before lumbar puncture had his arm prepared, thus avoiding even the slightest change in position and consequent disturbance of the manometer during venipuncture.[4]

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3. Only nine of the sixteen cases here reviewed are of this group; the other seven were cases of tabes, the only other cases available for the salt treatment at the time.

4. In three of these determinations Dr. F. E. B. Foley rendered, through his suggestions and cooperation, most valuable assistance.

In six cases studied thus there was a constant rise in pressure of from 30 to 50 mm. during the fifteen minutes occupied in giving the salt solution. A moment or two before the end of the injection the pressure would start down, and by thirty minutes after the end of the injection it would usually sink from 80 to 100 mm. below the original level. By this time the patients were invariably so uncomfortable that the lumbar puncture needle had to be withdrawn, which, of course, made further pressure observations impossible. However, the close correspondence in these initial pressure variations with those in the cat would make it reasonable to suppose that the depression increases till zero and possibly even negative levels are reached, as in the case of the cat.

Figure 1.

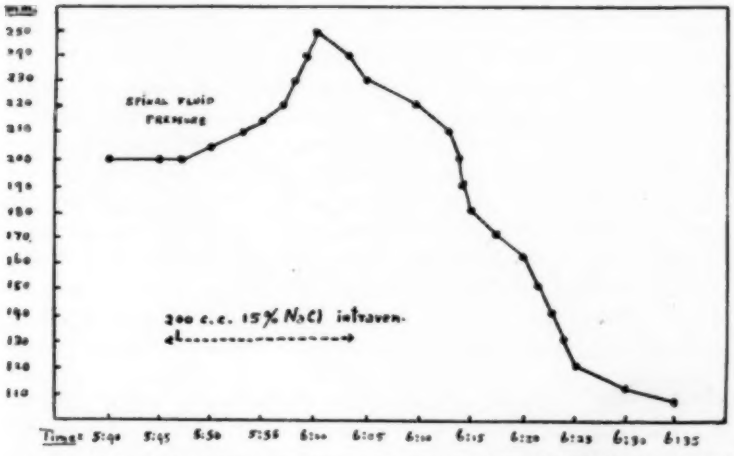

Fig. 1.—Vertical figures: pressure in mm. of cerebrospinal fluid. Horizontal figures: time. Dotted line: period during which 200 c.c. of 15 per cent. salt solution was given intravenously.

Normal pressures in the different cases often varied from 30 to 40 mm., but the relative changes after injection of salt solution have been remarkably constant. Figure 1 represents the course in one case quite typical of the group.

In view of these demonstrated pressure changes in man,[5] fluid displacement into the substance of the nervous system seemed an hypothesis reasonable enough to warrant the systematic use of salt

5. Three of these pressure determinations were carried out with Dr. F. E. B. Foley, and since charts of these will be published by him elsewhere, only one curve is reproduced here.

solutions in chosen cases of neurosyphilis, in an effort to render more effective arsphenamized serum distribution through the subarachnoid space.

PROPOSED CLINICAL PROCEDURE

It was decided that sixteen patients with neurosyphilis receiving intraspinal treatment [6] should receive 200 c. c. of 15 per cent. salt solution intravenously during the hour following intraspinal treatment, this to be repeated with each succeeding serum treatment, given at fortnightly intervals, till six salt injections had been given. Serologic and cytologic changes in the cerebrospinal fluid thus could be followed closely; with the return of the patients two months after the last treatment for follow-up examination and lumbar puncture, it would be possible to note any variation from the usual serological and clinical course of the cases.

ACTUAL CLINICAL COURSE OF THE PATIENTS GIVEN SALT SOLUTION

The actual procedure with the cases varied considerably from that planned, as will be apparent from a glance at Table 1, in which the results are tabulated. Only one patient in sixteen received all six proposed salt injections, three received five, five four, and the rest less. The reason for this deviation from schedule is apparent from Table 1. Five patients failed to return for completion of the course and were lost from observation. Six absolutely objected to completing the salt injections because of extreme distress produced by them on previous occasions. In five cases the Wassermann reaction and cell count became negative before the giving of all six injections of salt solution.

The column headed "subjective effect of salt," Table 1, shows that almost every patient experienced more or less marked discomfort from the hypertonic solutions, in six cases this discomfort being severe enough to necessitate abandoning subsequent injections. The symptoms associated with giving salt were surprisingly constant in all the cases; shortly after the start, marked facial flushing and a sensation of heat, involving first the face and then in succession neck, arms, trunk, legs

6. In this clinic the indications for intraspinal treatment are essentially those set forth by Fordyce [7] and others.[8]

7. Fordyce: The Treatment of Syphilis of the Nervous System, J. A. M. A. **63**:552 (Aug. 15) 1914; Intraspinal Therapy in Neurosyphilis, Am. J. Syph. **3**:337 (July) 1919.

8. Swift and Ellis: The Treatment of Syphilitic Affections of the Central Nervous System with Especial Reference to the Use of Intraspinous Injections, Arch. Int. Med. **12**:331 (Sept.) 1913; A Study of the Spirochaeticidal Action of the Serum of Patients Treated with Salvarsan, J. Exper. M. **18**:435 (Oct.) 1913.

TABLE 1.—Clinical Course of Patients Given Salt Solution

Diagnosis	Interval Since Primary	Reflexes*					Subjective Effect of Salt	Intraspinals Followed by Salt	Previous† Intraspinals: No Salt	Symptoms	Spinal Fluid Changes During Intraspinals‡				Reason for Incomplete Salts	Period of Observation, Mos.
											Wassermanns		Cell Counts			
		R	K	Ac	FN	B					O §	NaCl §	O §	NaCl §		
Neurosyphilis	10 yr.	A	P	P	P	A	Very distressing	2	2	Headache	C.c. C.c. 1.0++→1.8++	C.c. C.c. 1.8++→2.0++	20 → 15	15 → 5	Absent	4
Neurosyphilis	4 yr.	A	P	P	P	A	Very distressing	4	6	Headache	0.5++ 0.8++	0.8++ 1.0 —	40 18	18 7	Objected	7
Neurosyphilis	Unknown	A	P	P	P	A	Very distressing	4	6	Slight headache	0.2++ 0.6++	0.6++ 1.0++	25 12	12 10	Objected	7
Neurosyphilis	5 yr.	A	P	P	P	A	Very distressing	6	4	Nausea, vomiting	0.5++ 1.0++	1.0++ 2.0 —	104 50	50 10	.....	7
Neurosyphilis	10 yr.	A	P	P	P	P	Slightly distressing	1	3	Spastic gait	1.0++ 2.0++	2.0++ 2.0 —	14 10	10 8	Negative Wassermann	9
Neurosyphilis	2 yr.	A	P	P	P	A	Very distressing	2	4	Headache	1.2++ 2.0++	2.0++ 2.0 —	20 12	12 9	Negative Wassermann	5
Neurosyphilis	7 yr.	A	P	P	P	A	Slightly distressing	5	2	None	0.5++ 1.0++	1.0++ 0.8 —	20 9	9 9	Negative Wassermann	6
Neurosyphilis	20 yr.	A	P	P	P	A	Very distressing	5	22	Hot flashes	0.2++ 1.6+±	0.8++ 1.0++	60 10	9 9	Objected	15
Neurosyphilis	3 yr.	A	P	P	P	A	Slightly distressing	3	11	Nervousness	0.2++ 1.4 —	1.4 — 2.0 —	30 12	12 2	Negative Wassermann	9
Tabes.....	Unknown	P	A	A	P	A	Very distressing	2	2	Root pains	0.2++ 0.4++	0.3++ 0.4++	12 7	8 5	Absent	3
Tabes.....	8 yr.	A	A	A	P	A	Slightly distressing	5	3	Root pains	0.6++ 0.6++	0.7++ 1.2++	60 18	18 6	Objected	7
Tabes.....	Unknown	A	A	A	P	P	Very distressing	2	1	Ataxia	0.3++ 0.5++	0.5++ 0.6++	20 12	12 11	Objected	4
Tabes.....	35 yr.	P	A	A	A	A	Very distressing	3	5	Ataxia	0.5++ 1.2++	1.0++ 1.4+±	27 15	13 10	Absent	7
Tabes.....	12 yr.	A	A	A	A	A	No distress	4	4	Sensory	0.5+ + 0.8++	0.7++ 0.8++	15 7	8 5	Absent	6
Tabes.....	25 yr.	P	A	A	A	A	Very distressing	4	4	Ataxia	0.5++ 1.0++	1.0++ 1.4 —	30 15	12 9	Absent	7
Tabes.....	26 yr.	P	A	A	A	A	Very distressing	4	6	Ataxia	0.3++ 1.0++	1.0++ 1.8 —	10 3	2 2	Objected	8

* Reflexes: R, Romberg; K, knee-jerk; Ae, Achilles; FN, finger-nose; B, Babinski; P, present; A, absent.

† In this group it was planned to complete the intraspinal course in progress, giving salts, and then to give enough extra serum treatments to complete the set of six salts.

‡ These cell count and Wassermann figures include follow-up lumbar puncture two months after the last intraspinal treatment.

§ O, changes during intraspinal treatments without intravenous salt; NaCl, changes during intraspinal treatments with intravenous salts.

and feet; then intense dryness of the throat and at the end of the injection intense "boring" occipital or frontal headache, usually of only from ten to twenty minutes' duration, but relieved at the time by nothing except morphin.[9]

Comparison of cell count and Wassermann reaction improvement (Table 1) in patients receiving (a) intraspinal treatments alone and (b) intraspinal treatments plus salt solution intravenously would seem to indicate that the salt is of no therapeutic value.[10]

Furthermore, clinical evidences suggested that such use of hypertonic salt solutions might be positively harmful, for almost without exception there were aggravation of root pain and, in many instances, the occurrence of alimentary upsets persisting for four or five days during the intervals between treatments.

In view of these facts, it would seem that despite a sound theoretical basis, the use of hypertonic salt solution intravenously has no place in augmenting the intraspinal treatment of neurosyphilis. It may validly be objected that these observations are not conclusive, extending, as they do, rarely over nine months. However, it did not seem justifiable to push the work further in the face of no marked serological and cytological improvement and actual symptomatic retrogression.

EFFECT OF SALT INJECTIONS ON BLOOD PRESSURE, BLOOD AND URINE CHLORID

In Table 3 are tabulated the effects of intravenous injection of salt solutions on blood pressure, whole blood chlorid, and urine chlorid. The relation of these changes in a single case is shown in Figure 2. From Table 3 it is apparent that in this group immediately following the routine salt injections, there was from 51 to 61 per cent. increase in the whole blood chlorid, that an hour later the increase was from 20 to 35 per cent. Twelve hours after injection there was still from 14 to 22 per cent. elevation in blood chlorid; at that time approximately half of the injected salt had been excreted in the urine. In three cases (Nos. 5, 6 and 8, Table 3), because of previous disagreeable reaction to the routine dose of salt, smaller injections were given, with correspondingly less marked and prolonged elevation in blood chlorid. In one of these cases practically all of the injected salt had been excreted in the urine in twenty-two hours. In the other two cases excretion was not quite so rapid. In view of the marked and prolonged elevation in blood

9. The rate of giving the salt injections is shown in Figure 1.

10. Table 2 illustrates the course in one case which is quite typical of the series. It will be noted that the most striking change in the Wassermann reaction occurred on the day of the first salt injection which, of course, discredits the salt as being the effective agent in the subsequent unusually rapid improvement in the fluid.

chlorid in the cases receiving the routine salt injection, the triviality and transiency of the blood pressure changes is rather striking. It is worthy of special note that several of the determinations were made on the same patients at fortnightly intervals, and that in one such case the blood pressure levels were slightly lower during the second determination than during the first: Nos. 1 and 2 (Table 3) are consecutive determinations (eighteen day interval) on the same patient, and the average of the blood pressures during the first was 112/68, during the last 101/58.[11] These facts are of interest in view of the recent work on the relationship of hypertension and elevations in blood chlorid.

TABLE 2.—CLINICAL COURSE OF ONE CASE IN WHICH SALT SOLUTION WAS INJECTED

Date*	Treatment		Remarks	Reflexes	Spinal Fluid		
	Intravenous (Diarsenol in Gm.)	Intraspinal (50% diarsenolized Serum, C.c., and Diarsenol, Gm.)			Cells	Globulin	Wassermann
3/10/20	0.3	20 + 0.0002	No reaction	Negative	20	+	0.2 c.c. ++
3/17/20	0.4						
4/ 7/20	0.3	20 + 0.0003	Out of city since last treatment	Negative	18	+	0.4 c.c. ++
4/14/20	0.4						
4/21/20	0.3	20 + 0.0003	Symptom free	Negative	9	+	0.6 c.c. ++
5/ 5/20	0.4	20 + 0.0003	.....	Negative	9	+	0.6 c.c. ++
5/12/20	0.4						
5/19/20	0.3	20 + 0.0004	.....	Negative	7	±	0.8 c.c. ++
6/ 2/20	0.4						
6/17/20	0.4	20 + 0.0004	.....	Negative	7	+	0.8 c.c. ++
6/29/20	0.5	20 + 0.0004	.....	Negative	15	±	1.0 c.c. ++
7/13/20	0.4						
7/26/20	0.3	20 + 0.0002	.....	Negative	10	±	1.0 c.c. ++
8/10/20	0.3	20 + 0.0002	200 c.c. 15% salt solution intraven.	Negative	8	±	1.4 c.c. —
8/24/20	0.3	20 + 0.0003	Salt as above	Negative	7	±	2.0 c.c. —
9/10/20	0.3	20 + 0.0003	Salt as above	Negative	7	—	1.6 c.c. +±
9/25/20	0.3	20 + 0.0002	.....	Negative	5	—	2.0 c.c. —
Rest period							
12/17/20†	...	.....	.....	.....	3	—	2.0 c.c. —
Rest period							
3/ 1/21‡	...	.....	.....	.....	1	—	2.0 c.c. —
Rest period							

* The irregularity in treatment intervals is due to the fact that the patient was out of the city much of the time on business.

† Control lumbar puncture. Symptom free.

‡ Control lumbar puncture. Feels well.

With ten of the salt injections leukocyte counts were made immediately before and after injection, and the fresh and stained smears were examined at the same time. Red cells showed no morphologic evidence

11. The same general blood pressure tendency, though less striking, characterizes the consecutive determinations, Nos. 4, 5, and 6 (Table 3) and this despite the fact that the blood chlorid never got back to the original normal, once salt injections were started; the average of pressures in No. 6, though higher than in No. 5, is still lower than in the original determination, No. 4.

of injury; there were minor inconstant variations in the differential count, and in about half the cases a slight depression in the total white count. No effort was made to study variations in blood picture exhaustively.

SUMMARY AND CONCLUSIONS

1. Intravenous injections of 200 c.c. of 15 per cent. salt solution were given to six patients with neurosyphilis, with resulting disagreeable but not alarming symptoms. In these cases the cerebrospinal fluid pressure was found to rise sharply and then to fall, reaching a point about 100 mm. below the original level by thirty minutes after the end of the salt injection.

Figure 2.

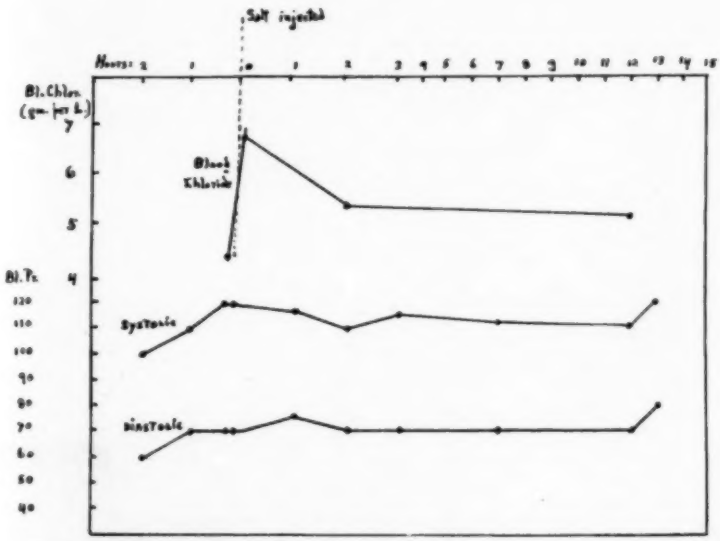

Fig. 2.—Upper left margin figures and top curve: whole blood chlorid in gm. per liter. Lower left margin figures and lower two curves: systolic and diastolic blood pressures. (During the three hours prior to injection, 200 c.c. urine were voided, containing 0.51 gm. salt; during the twenty hours after injection, 1,270 c.c. were voided containing 16.4 gm. salt.)

2. Salt injections were given according to a definite routine over a period of months, augmenting intraspinal treatment in a group of patients with neurosyphilis. There was no serologic or cytologic improvement over the usual course with intraspinal treatment alone, and symptoms were distinctly aggravated. Such injections hence would seem to have no therapeutic value in this group of neurosyphilis cases.

TABLE 3.—Effects of Intravenous Injection of Salt Solution on Blood Pressure, Blood and Urine Chlorids

No.	Amount 15% Salt Intravenous	Whole Blood Chlorid; (in Gm. per L. and Per Cent. Above Case normal§) With Reference to Salt Injection				Blood Pressure in (Mm. of Mercury) (i v = intravenous salt injection; i. s. = intraspinal injection)						Chlorids in Urine					
												Before Salt Injection			After Salt Injection		
		Before	After	2 Hrs. After	12 Hrs. After	2 Hrs. Before i. s.	Before i. s.	After i. s.	After i. v.	2 Hrs. After i. v.	12 Hrs. After i. v.	Volume Voided in C.c.	Period of Hours	NaCl, Gm.	Volume Voided in C.c.	Period of Hours	NaCl, Gm.
1	200 c.c.	4.4	6.8 54%	5.41 22%	5.2 18%	100 60	110 70	120 70	120 70	110 70	110 70	200	3	0.51	1,270	20	16.4
2*	200 c.c.	4.2	6.78 61%	5.36 27%	5.1 22%	95 55	100 55	86 50	110 65	110 65	110 60	120	2	0.77	1,540	22	17.8
3	200 c.c.	4.3	6.82 58%	5.38 25%	5.16 20%	110 60	115 65	115 70	115 70	115 65	115 60	90	2	0.80	990	14	9.6
4	200 c.c.	4.2	6.77 61%	5.69 35%	4.9 16%	110 65	112 70	110 65	140 80	125 80	112 70	110	3	0.46	1,700	20	10.8
5	170 c.c.	4.4	6.56 49%	5.34 21%	5.1 16%	110 65	110 60	110 60	120 65	115 60	110 65	230	3	0.53	1,600	15	10.0
6†	100 c.c.	4.8	6.13 27%	5.3 10%	4.9 0%	108 60	110 60	110 65	128 70	125 75	114 65	130	4	0.41	2,400	22	14.4
7	200 c.c.	4.5	6.81 51%	5.42 20%	5.14 14%	120 70	125 70	110 70	115 65	120 70	115 70	485	2	2.5	1,385	17	13.3
8	100 c.c.	4.6	5.08 %	5.1 11%	4.6 0%	110 60	110 60	115 60	120 65	125 70	110 60	600	9	4.8	840	14	11.76

* This determination and No. 1 were on the same patient, this one two and a half weeks later than No. 1.
† Two of the blood chlorid determinations were made by Miss Mary Redmond and she has checked several of the others.
‡ This determination was two weeks later than No. 5, which was in turn two weeks later than No. 4, all on the same patient.
§ By "normal" is meant the figure in the column "Before."

3. In a short series of cases whole blood chlorids were determined before and at intervals after salt injections, the output of salt in the urine was ascertained, and blood pressures were followed; immediately after the intravenous injection of 200 c. c. of 15 per cent. salt-solution the average whole blood chlorid elevation above normal (i.e., the first determination) was 57 per cent.; one hour later, 26 per cent.; twelve hours later, 18 per cent. In from seventeen to twenty-two hours, about half of the injected salt had been excreted in the urine. Variations in blood pressure were within physiologic limits.

A METABOLIC STUDY OF PROGRESSIVE PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY AND OTHER MUSCULAR ATROPHIES*

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We have recently had the opportunity to study the metabolism of nine cases of pseudohypertrophic muscular dystrophy in different stages of advancement. These cases will be reported from a clinical standpoint with about twenty more by Dr. R. V. Funsten. We also include some metabolic observations on other types of atrophic muscular involvement.

Endocrine disturbance in progressive pseudohypertrophic muscular dystrophy is indicated by (1) the hereditary character of the condition, (2) the metabolic abnormalities, (3) the occasional recovery at puberty when glandular readjustments occur, (4) reported improvement following endocrine therapy in some cases, and (5) the development of the disease in polyglandular dystrophies, notably in association with dystrophia adiposogenitalis. Necropsy findings with special reference to the ductless glands are urgently needed to elucidate further the pathogenesis of the condition.

The symptomatology and the pathologic changes have been well reviewed by Timme[1] and by Janney, Goodhart, and Isaacson.[2] Involvement of the pineal gland has been suggested by Timme from a study of the literature and from roentgen-ray examinations in three cases from the same family; pineal shadows were evident in two cases only of the series of nine studied by Janney, Goodhart, and Isaacson. These last named investigators, as does McCrudden,[3] attribute the condition to endocrine dysfunction affecting carbohydrate metabolism.

According to McCrudden, there is hypoglycemia, no increased heat formation, a rapid fall in blood sugar during the first twenty-four hours of starvation indicative of a diminished glycogen reserve, increas-

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1. Timme, W.: Arch. Int. Med. **19**:79 (Jan.) 1917.
2. Janney, N. W.; Goodhart, S. P., and Isaacson, V. I.: Arch. Int. Med. **21**:188 (Feb.) 1918.
3. McCrudden, F. H.: Arch. Int. Med. **21**:256 (Feb.) 1918; J. A. M. A. **70**:1216 (April 27) 1918.

ing "fatty degeneration," an increased respiratory quotient, and lipemia. Since a prompt and marked rise in blood sugar follows the administration of epinephrin, the impaired glycogenesis is associated with damage to the suprarenals rather than to the liver.

One of our patients (Case 5) died of influenzal pneumonia and a necropsy was obtained. This was a polyglandular condition, Fröhlich's syndrome complicating the picture of progressive pseudohypertrophic muscular dystrophy. Through oversight, the pineal gland was not preserved for microscopic examination. The following description is abstracted from Dr. E. M. Medlar's records.

On gross examination, the suprarenals were apparently larger, though thinner than normal, with a very small medullary substance and a thin cortical layer. The thyroid was slightly hypertrophied and there was considerable colloid. The parathyroids (four, the size of small peas) were reddish in color; on section, they seemed to be made up of small round bodies. The pituitary contained a cyst filled with a clear fluid; the cyst was about 0.5 cm. in diameter; the remaining tissue was flattened and less in amount than normal.

Microscopic examination revealed that the bodies taken to be parathyroids consisted of acini filled with colloid material; "if these bodies are accessory thyroids, the parathyroids were so small that they could not be detected in gross." Sections of the pituitary showed a small cyst in the pituitary lobe, with an apparent marked increase in the secretory cells (and secretion) of the anterior lobe. Thyroid, thymus and pancreas exhibited little or no change, except that for the last two there was an ingrowth of fat tissue. The adrenals were congested, and there were areas of necrosis with infiltration of leukocytes in the cortex.

The muscle tissue showed the fatty infiltration and atrophy as described for pseudohypertrophic muscular dystrophy. It is of incidental interest that the respiratory muscles were less atrophied than the others, indicating a selective conservation of this group.

Because of the muscular changes, a study of the creatinin elimination in the muscular atrophies was made by Spriggs [4]; he observed a lowered creatinin excretion in pseudohypertrophic muscular dystrophy, in myotonia congenita, and in myasthenia gravis. Levene and Kristeller [5] determined the creatinin and creatin elimination in several types of muscular involvement, including five cases of muscular dystrophy, on high and low protein intakes; cases with considerable loss of muscular function gave a much diminished creatinin output and a creatinuria. In conditions of muscular atrophy or dystrophy practically 90 per cent. of ingested creatin (in beef) reappeared in the urine.

McCrudden and Sargent [6] found the daily creatinin excretion to be normal and constant (1.5 gm. or 22.6 mg. per kilogram of body weight) and a creatinuria (about 0.5 gm. daily) in a male, aged 33

4. Spriggs, E. I.: Biochem. Ztschr. **2**:206, 1907.
5. Levene, P. A., and Kristeller, L.: Am. J. Physiol. **24**:45, 1907.
6. McCrudden, F. H., and Sargent, C. S.: Arch. Int. Med. **17**:465 (April) 1916; **21**:252 (Feb.) 1918.

years. There was a low ammonia. Total nitrogen, uric acid, and calcium and magnesium elimination were normal, though the ratio calcium: magnesium was a little high. Blood findings were: creatinin, 1.43 mg.; creatin, 3.86 mg.; nonprotein nitrogen, 28.9 mg.; uric acid, 2.3 mg.; glucose, 0.075 per cent.; and cholesterol, from 0.05 to 0.144 per cent. They state that the metabolic picture is distinctly different in progressive muscular atrophy (two cases) in which there is creatinuria and normal blood sugar, and in myasthenia gravis (two cases) in which there is hypoglycemia without creatinuria.

The nine cases reported by Janney, Goodhart, and Isaacson were in patients in advanced stages of the disease, and from 11 to 48 years of age; one female case is included. They found a marked decrease in the urinary creatinin, creatinuria, hypoglycemia, normal blood urea, low blood creatinin, and normal (?) blood creatin. There was a retention of calcium and magnesium when the calcium content of the diet was adequate. Of importance is the delayed utilization of glucose for five cases when ingested (1.75 gm. glucose per kilogram of body weight).

Brock and Kay [7] have presented three adult cases of endocrinopathies associated with unusual manifestations in the muscular system. One was a case of dystrophia adiposogenitalis with a recent limited muscular dystrophy. This case showed a creatinuria, hypoglycemia, and a delayed glycogenesis without glycosuria following glucose ingestion. A. Gibson [8] has reported a case of familial "muscular infantilism" in an adult male. There was creatinuria, though histologic examination of the muscle showed but little departure from the normal. Blood sugar findings resembled the results we have obtained for our two adult cases of pseudohypertrophic muscular dystrophy.

Pemberton [9] has reported a somewhat lowered creatinin elimination and a negative calcium balance in myasthenia gravis, and a very low creatinin and slightly negative calcium balance in myotonia atrophica. Diller and Rosenbloom [10] obtained similar results for a case of myasthenia gravis; there was no creatinuria. Rosenbloom and Cohoe [11] found a normal nitrogen partition in myotonia congenita (Thompsen's disease); there was a negative calcium balance. Three studies of the metabolism in amyotonia congenita (Oppenheim's disease) in children are found in the modern literature; Gittings and Pemberton [12] reported a very low creatinin excretion in a boy 21 months old, with

7. Brock, S., and Kay, W. E.: Arch. Int. Med. **27**:1 (Jan.) 1921.
8. Gibson, A.: Arch. Int. Med. **27**:338 (March) 1921.
9. Pemberton, R.: Am. J. M. Sc. **139**:816, 1910; **141**:253, 1911.
10. Diller, T., and Rosenbloom, J.: Am. J. M. Sc. **143**:65, 1914.
11. Rosenbloom, J., and Cohoe, B. A.: Arch. Int. Med. **14**:263 (Aug.) 1914.
12. Gittings, J. C., and Pemberton, R.: Am. J. M. Sc. **144**:732, 1912.

no disturbance of the calcium elimination; Powis and Raper [13] obtained low creatinin and high creatin figures for a girl 4 years of age, ingested creatin being promptly eliminated, and calcium and potassium retention being normal; and Ziegler and Pearce [14] found low creatinin and high creatin values, normal uric acid, an increased undetermined nitrogen and neutral sulphur, blood glucose of 0.14 per cent., and blood creatin and creatin of 1.5 and 5.45 mg. respectively.

The nine cases of progressive pseudohypertrophic muscular dystrophy included in this report comprise: Two cases in young boys in which the atrophy was moderately advanced. Three cases in older boys (one with a coincident dystrophia adiposogenitalis) in which the muscular atrophy had progressed until movements were practically limited to the muscles of the thorax, distal upper extremities, neck, and face; and two male adult cases, the condition developing after puberty and progressing slowly, with muscular pseudohypertrophy, lordosis, and general weakness. Of particular interest from a comparative metabolic standpoint is the fact that two of the patients in the series were brothers, one with a moderately advanced case and the other presenting marked atrophic changes. One case of myasthenia gravis, one of muscular atrophy following acute anterior poliomyelitis, and one of myositis ossificans are also included. These three cases were adult males also.

Each case was transferred to our special metabolism unit for study. The diet was nonpurin and noncreatin, the constituents being kept essentially the same daily. The protein intake was set at a figure slightly above the physiologic requirement only, inasmuch as the literature on creatinuria indicates that an increased protein metabolism may be accompanied by a greater creatin elimination, a fact which we have verified in some of our cases.[15] Blood sugar determinations were made according to the Benedict modification of the Lewis-Benedict method: other analyses were made by the current procedures. Blood samples for Case 6 could only be obtained from the jugular vein. It was impossible to do a satisfactory venepuncture in the myositis ossificans case, and in Case 5, though micro-sugar determinations were made for the latter with 0.04 c. mm. of blood, centrifuging the precipitates, and using similar Sahli hemoglobinometer tubes as a dilution colorimeter.

Levene and Kristeller have pointed out that the creatinin elimination in muscular atrophy cases does not have the same constancy that obtains in the normal individual. From data obtained in our patients, we find this to be decidedly the case, the twenty-four hour collection

13. Powis, F., and Raper, H. S.: Quart. J. M. **10**:7, 1916.
14. Ziegler, M. R., and Pearce, N. O.: J. Biol. Chem. **42**:581, 1920.
15. Gibson, R. B., and Martin, Francis T.: J. Biol Chem. **41**: xxxvi, 1920.

of the urinary specimens being absolutely assured. However, we have found it possible to stabilize the creatinin excretion under constant conditions of diet over periods of several days.

A summary of the ages, weights, creatinin coefficients, and blood findings is given in Table 1. Brief clinical descriptions and the nitrogen partition in tabular form are presented also for the individual cases.

TABLE 1.—CREATININ AND CREATIN COEFFICIENTS, AND BLOOD ANALYSES OF TWELVE CASES

	Age in Years	Weight, Kg.	Creatinin Coefficient	Total Creatinin Coefficient	Ingested Creatin, % Recovered	Blood Sugar Control, %	Glycogenesis Test Blood Sugar, %	Blood Creatinin, Mg. %	Blood Creatin, Mg. %	Blood Fat, %	Blood Cholesterol, per Cent.	Blood Calcium, Mg. %	Hydrogen Ion Concentration
1. E. T.	5	18.0	5.2	9.0	48	0.070	0.098	0.75	10.2	0.61	....	....	...
2. D. R.	8	21.8	5.0	11.5	32	0.071	0.067	0.45	5.7	0.89	....	....	...
3. J. Schw. Adm. 1..	5	18.2	2.5	4.3	30	0.080	0.174	0.91	7.6	0.59	....	....	7.5
Adm. 2..	6	20.0	2.6	5.6	..	0.067	0.101	....	....	....	....	....	...
4. R. Stol. Adm. 1...	9	20.0	2.1	5.9	90	0.112	0.101	0.60	7.2	0.67	0.29	....	...
						0.119	0.115	1.06	7.5	0.57	0.28	....	...
5. O. Schaf.	15	90.0	1.0	3.4	70	0.080	0.178	....	....	....	....	....	...
6. Wm Schw. Adm. 1	15	21.3	1.0	3.7	80	0.089	0.160	0.76	5.7	0.61	....	....	7.6
Adm. 2	15	....	1.6	7.5	..	0.117	0.198	0.53	9.7	0.50	0.18	....	...
7. W. Stll.	12	30.6	1.7	5.0	100	0.125	0.147	0.50	7.0	....	....	....	...
						0.082	0.124	0.50	15.6	0.95	....	....	...
8. B. McD.	22	55.0	7.1	7.7	40	0.133	0.157	....	15.1	....	....	10.1	...
						0.116	0.143	2.45	12.9	....	....	....	...
								1.9	30.0	0.62	0.22	11.5	...
9. O. Sm.	38	50.0	4.2	5.7	...	0.101	0.123	1.0	12.1	0.51	0.27	12.6	...
10. Geo. S.	48	79.0	7.1	7.1	...	0.106	.....	0.74	5.2	....	....	....	...
						0.125	0.185	1.4	7.7	....	....	....	...
11. L. W.	25	63.0	7.6	8.2	60	0.112	0.111	1.25	6.8	0.72	0.22	....	...
12. Geo. F.	26	54.0	5.3	5.3	...	.....	.....	....	....	....	....	....	...

Cases 1 to 9, inclusive, were pseudohypertrophic muscular dystrophy patients; Case 10 had myasthenia gravis; Case 11 muscular atrophy due to anterior poliomyelitis, and Case 12 myositis ossificans.

In the cases in the earlier stage of progressive pseudohypertrophic muscular dystrophy (Cases 1 and 2), there was creatinuria; this is a normal condition in childhood (Rose [16]). Shaffer [17] gives the creatinin coefficient for normal children as between 3.3 and 6.5, and for adults from 8.1 to 11.0. We regard creatinin coefficients of 5.2 and 5.0 for Cases 1 and 2 as a low normal. Ingested creatin (0.5 gm.) was destroyed only in part, 48 and 32 per cent., respectively, being recovered. Krause's [18] normal cases, given 0.3 gm. creatin by mouth, eliminated the following percentages; girl of 6 years, 56; boy of 8 years, 43; girl of 11 years, 31. The recovery of ingested creatin in our two cases is not to be regarded as abnormal. A rather high uric acid nitrogen for Case 2 was observed. Total nitrogen figures were quite low, and positive nitrogen balances are indicated. There was hypoglycemia in

16. Rose, W. C.: J. Biol. Chem. **10**:265, 1911.
17. Shaffer, P. A.: Am. J. Physiol. **23**:1, 1908.
18. Krause, R. A.: Quart. J. Physiol. **8**:87, 1913.

both cases. Diminished glycogenesis (Janney) and high blood creatin obtained for Case 1; normal blood creatin figures for children are not yet established satisfactorily, though Veeder and Johnston[19] found from 2.2 to 7.2 mg. with a mean for the nonextreme cases of 3.8.

Still lower creatinin coefficients (2.5 and 2.1) were obtained for Cases 3 and 4; in these boys, the muscular changes were more pronounced than for the previous group. There was creatinuria in both cases. Hypoglycemia and diminished glycogenesis were found for Case 3, but not for Case 4. Case 4 was clinically the more advanced, and this is reflected by the lower creatinin coefficient and the much greater recovery of ingested creatin.

Cases 5, 6, and 7 were older boys of 15, 15, and 12 years, respectively. There were most pronounced atrophic changes of the muscular system. Strikingly low creatinin excretion and creatinin coefficients (1.0 to 1.6) were obtained; however, the creatinin coefficient of Case 5 (with Fröhlich's syndrome) is based on a body weight of 90 kg. There was creatinuria, and ingested creatin was largely recovered, completely so for Case 7. Hypoglycemia was observed, though normal blood sugars have been obtained also for Cases 6 and 7. Glycogenesis was reduced; glycosuria followed the glucose ingestion (100 gm.) for Case 5. High blood creatins have been noted for Cases 6 and 7. The high blood fat for Case 7 is probably accounted for by an excessive diet. Case 6 was a brother of Case 3.

The adult pseudohypertrophic muscular dystrophy cases (Cases 8 and 9) present some differences that are noteworthy. The metabolic disturbance is not so intense. Case 9 presented a greater atrophic change with a much less creatinin coefficient and a greater creatinuria than Case 8. In fact, there was little or no creatinuria on some days for Case 8. Forty per cent. of ingested creatin (1 gm.) was excreted by Case 8. For Case 9, there was an increased creatin excretion following creatin ingestion at least over 40 per cent., but the metabolism was not stabilized, and the result was unsatisfactory. In the normal male adult, ingested creatin disappears. Normal blood sugar obtained for Case 8 (0.116 and 0.133) and a low normal figure (0.101) for Benedict's method was found in Case 9. Both patients showed a somewhat deficient glycogenesis without glycosuria following glucose ingestion (100 gm.). High blood creatinin and very high creatin were observed for Case 8, and high blood creatin for Case 9.

Such figures as we have obtained for blood fat (except as noted), blood cholesterol, hydrogen ion concentration of the blood, and plasma calcium are not to be regarded as significant.

19. Veeder, B. S., and Johnston, M. R.: Am. J. Dis. Child. **12**:136 (Aug.) 1916.

We found, as did McCrudden, no creatinuria in myasthenia gravis (Case 10). A rather low creatinin coefficient (7.1) was observed. There was a normal blood sugar rather than a hypoglycemia and a delayed storage of ingested glucose. Incidentally, combined therapy with calcium lactate, caffein citrate, desiccated whole pituitary substance, and epinephrin injections over a month resulted in no clinical improvement.

In the case of muscular atrophy resulting from acute anterior poliomyelitis in an adult (Case 11), there was creatinuria, a somewhat lowered creatinin coefficint of 7.6, and 58 per cent. of ingested creatin (1 gm.) was recovered. Normal blood sugar and glycogenesis were found.

A case of myositis ossificans (Case 12) is included in the present series. The metabolic picture is characterized by a high uric acid nitrogen, a low creatinin (coefficient 5.2), and no creatinuria. There was a daily nitrogen retention of 2.28 gm. and positive balances for calcium of 1.14 gm. and for magnesium of 0.46 gm. over a five day period.

Inasmuch as carbohydrate deficiency induces creatinuria (Mendel and Rose [20]), it has been argued that the faulty carbohydrate metabolism is responsible for the creatinuria in progressive pseudohypertrophic muscular dystrophy. We are inclined to believe that the atrophic dysfunction and actual diminution of the amount of muscle tissue are the conditions inducing the creatinuria, just as in the non-endocrine muscular atrophies where the carbohydrate metabolism is normal as in Case 11. The lowest creatinin coefficients occur in those cases in which the greatest muscular atrophy has occurred; likewise, the recovery of ingested creatin is greatest in the advanced cases. The creatinin and creatin figures are not particularly abnormal in the earlier atrophic changes of the disease, though the endocrine disturbance must be well established at that time. Again normal blood sugar may be obtained in the muscle dystrophy cases (Cases 4, 8 and 9; see also Cases 6 and 7) and even normal glycogenesis may be observed (Cases 2 and 4).

From the literature and our own observations, then, the outstanding metabolic features of progressive pseudohypertrophic muscular dystrophy are:

1. Those associated with the atrophic condition of the muscles, and which are intensified as the atrophy progresses:

1. Lowered creatinin excretion and creatinin coefficient.
2. Creatinuria.
3. Recovery in the urine of ingested creatin.
4. Creatinemia, though high blood creatins are not a constant finding.

20. Mendel, L. B., and Rose, W. C.: J. Biol. Chem. **10**:213, 1912.

2. Disturbances of carbohydrate metabolism of endocrine origin, usual but not constant findings.

1. Hypoglycemia.

2. Deficient glycogenesis following moderate glucose ingestion, and commonly without glycosuria.

The differential diagnosis of progressive pseudohypertrophic muscular dystrophy, myasthenia gravis, and progressive muscular atrophy may be checked according to McCrudden's suggestion by the metabolic and blood findings. The characteristic differences to be expected, with the addition of the glucose tolerance, are summarized as follows:

	Creatinuria	Blood Glucose	Glucose Tolerance
Progressive pseudohypertrophic muscular dystrophy	Present	Low	Diminished
Myasthenia gravis	Absent	Low or normal	Diminished
Progressive muscular atrophy	Present	Normal	Normal

There is little evidence on which to base a satisfactory therapeutic procedure for progressive pseudohypertrophic muscular dystrophy. McCrudden reports improvement in his case as the result of pituitary extract and epinephrin treatment, and a return of the blood sugar to normal. One patient (Case 1) in this series has apparently recovered, according to Dr. Steindler, so far as physical examination and strength tests may be depended on; we have not had the chance to make a further metabolic study. Whether or not the recovery was spontaneous with the prevention of overexertion and an adequate diet, or due to therapy with calcium lactate (0.3 gm., t.i.d.) is undetermined; calcium therapy was employed because of the suggested part it plays in carbohydrate metabolism (Underhill and Blatherwick [21]) and the reported favorable influence in other obscure myopathies. One patient (Case 3) has not improved on calcium lactate and dried whole pituitary gland. Pituitary extract (Parke, Davis, and Co., pituitrin, obstetric preparation) injections given daily for six weeks to one patient (Case 8) had little or no effect. All of the patients gained in weight and improved somewhat under conditions of hospitalization.

SUMMARY AND CONCLUSIONS

Seven cases of progressive pseudohypertrophic muscular dystrophy in boys and two adult male cases have been studied. One case each of myasthenia gravis, muscular atrophy following acute anterior poliomyelitis, and myositis ossificans are included in this report.

The progress of the atrophic condition of the muscular system in progressive pseudohypertrophic muscular dystrophy is indicated metabolically by a diminishing creatinin excretion and creatinin coefficient,

21. Underhill, F. P., and Blatherwick, N. R.: J. Biol. Chem. **19**:119, 1914.

by the creatinuria, and by the incomplete destruction of ingested creatin. The creatinin—creatin picture is quite similar to that in muscular atrophy where there is no disturbance of carbohydrate metabolism.

While hypoglycemia and deficient glycogenesis are characteristic for progressive pseudohypertrophic muscular dystrophy, normal blood sugar figures may be obtained, and normal glycogenesis may occur even when hypoglycemia is present.

McCrudden's metabolic differentiation (with the addition of glucose tolerance findings) of progressive pseudohypertrophic muscular dystrophy, myasthenia gravis, and progressive muscular atrophy is essentially confirmed and should be of value in the diagnosis of these conditions.

In a case of myositis ossificans, we have observed a diminished creatinin excretion without creatinuria, an increased output of uric acid, and positive nitrogen, calcium, and magnesium balances.

Apparent recovery over a period of a few months is reported in an early recognized typical case of progressive pseudohypertrophic muscular dystrophy. This case was a boy, 5 years of age.

The need of a study of the necropsy findings with special reference to the ductless glands in pseudohypertrophic muscular dystrophy is emphasized.

We are indebted to Dr. Arthur Steindler, who has referred several of the cases in this series to this laboratory for study.

The diets were calculated and prepared under the supervision of Miss Gertrude Whiteford and Miss Lela E. Booher.

ADDENDUM

Since this paper was written, we have studied another case of pseudohypertrophic muscular dystrophy in a boy, 10 years of age. The findings in this case bear out our contentions regarding the creatin and carbohydrate metabolism. The patient presented the characteristic picture of the disease; the atrophy had progressed to a stage intermediate between Cases 3 and 4. The clinical history and nitrogen metabolism are given under Case 13.

The creatinin coefficient was 2.2 and the total creatinin (creatinin plus creatin) coefficient was 5.6. About 60 per cent. of the 0.5 gm. creatin given by mouth was recovered for that day. Blood sugar was 0.144 per cent. and two hours after the ingestion of 44 gm. glucose it was 0.138 per cent., with the hourly urines negative for sugar. There was, therefore, a hyperglycemia and a normal sugar tolerance. Blood creatinin was 1.1 mg. and blood creatin was 5.2 mg. per hundred c.c. Blood cholesterol was 0.22 per cent. The basal metabolic rate was 51.8 calories per square meter of body surface per hour; the expected normal was 52 calories. The respiratory quotient was 0.85.

REPORT OF CASES

CASE 1.—*Progressive pseudohypertrophic muscular dystrophy.*

E. T., white, male, 55 years of age, weight 18 kg. The condition was first noticed a month previous to admission to the hospital. He had always seemed normal, though easily fatigued. This patient has since discharge apparently recovered.

There was muscular atrophy as follows: adductors of the thumb; muscles of the thenar and hypothenar groups; muscles of the shoulder girdle; long muscles of the back; gluteal muscles; thigh muscles, and calf muscles. Histological examination of the muscle was characteristic for pseudohypertrophic dystrophy.

The case was transferred to the metabolism unit Oct. 22, 1919, and put on a nonpurin and noncreatin diet of 30 gm. protein, 37 gm. fat, and 125 gm. carbohydrate, the total calories being 1,000.

TABLE 2.—URINE NITROGEN PARTITION (CASE 1)

Day	Total N	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N		Remarks
	Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
10/23	4.03	3.57	88.5	0.215	5.34	0.065	1.61	0.098	2.43	0.061	1.53	In bed
10/24	4.35	3.89	89.3	0.210	4.83	0.060	1.38	0.093	2.14	0.067	1.54	Active
10/25	3.96	3.43	86.5	0.195	4.92	0.058	1.47	0.089	2.25	0.066	1.66	Active
10/26	3.50	2.98	85.0	0.265	7.57	0.073	2.08	0.093	2.66	0.155	4.53	0.5 gm. creatin
10/27	3.50	2.64	75.4	0.262	7.49	0.068	1.66	0.089	2.54	0.055	1.57	

CASE 2.—*Progressive pseudohypertrophic muscular dystrophy.*

D. R., white, male, 8 years of age, weight 21.8 kg. The patient first walked at 3 years of age, but could not turn. He tired easily. The condition was progressive. He was admitted to this hospital Nov. 17, 1919.

The patient had a distinctly asthenic gait; he walked with the legs abducted. There was contracture of the tendo Achillis of each leg, and the left foot showed a tendency to varus. Both calves were unusually developed. The muscles of the arms and back seemed normal.

While in the metabolism unit, he was on a diet of 35 gm protein, 45 gm. fat, and 115 gm. carbohydrate, with a caloric value of 1,000.

TABLE 3.—URINE NITROGEN PARTITION (CASE 2)

Day	Total N	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N		Remarks
	Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
10/19	5.49	4.59	83.6	0.454	8.27	0.095	1.73	0.110	2.00	0.144	2.63	In bed
10/20	6.51	4.41	67.7	0.460	7.07	0.108	1.65	0.105	1.61	0.143	2.24	Active
10/21	4.76	3.72	78.1	0.335	7.04	0.103	2.17	0.114	2.51	0.196	4.00	0.5 gm. creatin
10/22	6.37	3.69	57.9	0.461	7.24	0.121	1.90	0.109	1.71	0.095	1.49	

CASE 3.—*Progressive pseudohypertrophic muscular dystrophy.*

J. Schw., white, male, 6 years of age, weight 18.2 kg. The condition was noted at the time he began to walk, and was characterized by progressive muscular weakness. At the time of admission, the patient was unable to get up stairs, and had to brace himself when he got up from the floor.

There was a decided ataxic gait. The calf muscles were much enlarged. The arms were notably weakened. Lordosis was present.

Three boys by an earlier marriage of the mother had been similarly affected and died. An older brother of this patient by her present husband is one of our series (Case 66). One girl by the first marriage and two by the second are alive and well.

This case was under observation in the summer of 1919, and again in the winter of 1919-1920. Urinary nitrogen partition figures are given for the second admission. The diet was nonpurin and noncreatin. There were 30 gm. protein, 40 gm. fat and 150 gm. carbohydrate, with a total of 1,039 calories.

TABLE 4.—URINE NITROGEN PARTITION (CASE 3)

Day	Total N, Gm.	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N	
		Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%
12/14	4.97	....	....	.....	....	0.091	1.83	0.048	0.97	0.089	1 79
12/15	4.55	....	....	.....	....	0.092	2.02	0.051	1.12	0.071	1.56
12/16	5.30	3.35	62.0	0.398	7.38	0 129	2.40	0.048	0.89	0 055	1.02
12/17	4.55	3.51	77.2	0.371	8.15	0.136	2.99	0.054	1.19	0.070	1.54
12/18	4.13	3.31	80.2	0.230	6.27	0.117	2.83	0.053	1.28	0 062	1.50
12/19	4.16	2.94	70.7	0.288	6.92	0.101	2.43	0.053	1.27	0.051	1.23

CASE 4.—*Progressive pseudohypertrophic muscular dystrophy.*

R. S., white, male, 9 years of age, weight 20 kg. The patient walked first at 2.5 years. The previous history of his illness was typical.

The patient walked with a peculiar gait, stumbled a great deal, but could get about slowly. He would get up from the floor only with difficulty, using the hands on the thighs; at times he could not get up unless assisted. The legs were weak and the ankles turned outward. There was lordosis, the scapulae were winged, and the calf muscles were pseudohypertrophied.

He was placed on a diet consisting of 32 gm. protein, 45 gm. fat, and 150 gm. carbohydrate, making a total of 1,165 calories, for a period from December 2 to Dec. 9, 1920. He was in the metabolism unit again during a second admission (Jan. 14, 1921) for an additional glucose tolerance test only.

TABLE 5.—URINE NITROGEN PARTITION (CASE 4)

Day	Total N Gm.	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N		Remarks
		Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
12/4	2.23	....	....	.....	....	0.072	3.23	0.042	1.88	0.036	1.61	
12/5	2.39	1.82	76.2	0.143	5.98	0.080	3.35	0.045	1.89	0.039	1.71	
12/6	2.00	1.49	74.8	0.105	5.26	0.098	4.91	0.035	1.75	0.029	1.46	
12/7	2.31	1.62	70.1	0.126	5.46	0.112	4.85	0.041	1.77	0.049	2.13	
12/8	2.70	1.99	73.7	0.102	3.78	0.125	4.64	0.051	1.89	0.145	5.38	0.5 gm. creatin
12/9	2.50	1.92	76.8	0.105	4.20	0.089	3.56	0.053	2.12	0.082	3.28	

The sulphur partition was determined on a composite sample of the urines for December 4 and 5. The results are given as grams of SO_3 per day

Total S, Gm.	Inorganic S		Ethereal S		Neutral S	
	Gm.	%	Gm.	%	Gm.	%
0.508	0.393	77.4	0.072	14.2	0.042	8.3

CASE 5.—*Progressive pseudohypertrophic muscular dystrophy; dystrophia adiposogenitalis (Frölich's syndrome).*

O. Schaf., white, male, 15 years old, height 140 cm., weight 90 kg. The condition was first noted eleven years previous to admission to the hospital (Nov. 28, 1919). He had not walked for three years. A sister is similarly affected. The patient died of influenzal pneumonia. The necropsy findings are discussed elsewhere in this paper.

The facies were typical for dystrophia adiposogenitalis. The muscles of the extremities, the thigh group, and the psoas appeared large and flabby. Flexion and extension of the arms, forearms, thighs and feet were little or

nil. The calf muscles were a fourth normal strength. On roentgen-ray examination, the sella turcica was irregular and indefinitely outlined; the anteroposterior diameter was 14 mm., the superior-inferior diameter 9 mm.

The patient was given a diet comprising 75 gm. protein, 70 gm. fat and 190 gm. carbohydrate, with a calorific value of 1,700.

TABLE 6.—URINE NITROGEN PARTITION (CASE 5)

Day	Total N	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N		Remarks
	Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
12/ 6	7.14	5.03	70.4	0.703	9.85	0.133	1.86	0.129	1.84	0.166	2.29	
12/ 7	7.70	5.17	67.1	0.508	6.53	0.171	2.22	0.075	0.97	0.250	3.25	
12/ 8	7.35	5.48	74.5	0.677	9.21	0.139	1.89	0.122	1.66	0.169	2.30	
12/ 9	8.23	5.87	71.3	0.706	8.58	0.172	2.09	0.082	0.99	0.218	2.65	
12/10	6.23	4.70	75.4	0.616	9.89	0.175	2.81	0.089	1.42	0.366	6.28	0.6 gm. creatin
12/12	9.06	6.54	72.1	0.687	7.58	0.208	2.30	0.092	1.02	0.269	2.96	
12/13	9.072	7.75	85.4	0.643	7.09	0.184	2.18	0.098	1.08	0.216	2.38	
12/19	9.02	7.24	80.3	0.538	5.97	0.190	2.10	0.079	0.88	0.278	3.08	
12/20	9.41	7.36	78.3	0.523	5.55	0.190	2.02	0.080	0.85	0.262	2.79	

CASE 6.—*Progressive pseudohypertrophic muscular dystrophy.*

Wm. Schw., white, male, 15 years of age, weight 21.3 kg. The condition was first noticed seven years previous to the first admission to the hospital (July 8, 1919). The history of the progress of the disease was typical. This case was an older brother to Case 3.

The patient could not walk. The muscular system was extremely atrophied, and there were contractures of the feet, knees, and flexion contracture of the hips. There was no motion in the shoulders, knees and hips, and but slight motion in the elbows and fingers. The back was considerably curved.

The urinary nitrogen figures below were obtained on the second admission. The diet for December 13-19 contained 30 gm. protein, 40 gm. fat and 150 gm. carbohydrate, with an energy value of 1,080 calories; for the later period, January 20-22, the patient was given 40 gm. protein, 40 gm. fat, and 150 gm. carbohydrate, equivalent to 1,120 calories. At this time he weighed 22.7 kg.

TABLE 7.—URINE NITROGEN PARTITION (CASE 6)

Day	Total N,	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N	
	Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%
12/13	4.20	2.64	62.9	0.363	8.64	0.109	2.60	0.029	0.69	0.122	2.91
12/14	3.99	3.13	78.4	0.440	11.0	0.136	3.41	0.027	0.68	0.111	2.78
12/17	4.90	2.59	52.9	0.384	7.84	0.125	2.47	0.028	0.57	0.160	3.27
12/18	3.78	2.56	67.7	0.280	7.41	0.122	3.23	0.030	0.79	0.149	3.95
12/19	4.30	3.34	79.5	0.298	6.98	0.123	2.93	0.033	0.79	0.153	3.64
1/20	5.04	3.53	70.0	0.321	6.37	.....	....	0.031	0.62	0 129	2.55
1/21	5.51	4.20	76.0	0.265	4.81	.....	....	0.033	0.60	0.126	2.29
1/22	4.97	3.76	75.6	0.367	7.36	.....	....	0.032	0.64	0 131	2 64

CASE 7.—*Progressive pseudohypertrophic muscular dystrophy.*

W. Stil., white, male, 12 years of age, weight 30.5 kg. The condition was first noted four years before admission (Sept. 5, 1919). The patient had not walked for two years. There was no familial history of the disease.

There was general muscular weakness, marked muscular atrophy (especially of the deltoids), and contractures of the hamstrings, toes and hips. The calf muscles showed the characteristic pseudohypertrophy.

The patient was observed for three months in the metabolism unit. At the time of his discharge he weighed 39 kg. The diet given for the metabolic period tabulated in Table 8 consisted of 32 gm. protein, 75 gm. fat and 200 gm. carbohydrate; the energy value was 1,600 calories.

TABLE 8.—URINE NITROGEN PARTITION (CASE 7)

Day	Total N	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N		Remarks
	Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
10/12	3.98	2.20	55.2	0.362	9.10	0.098	2.46	0.054	1.35	0.095	2.41	
10/13	3.01	2.16	71.4	0.228	7.91	0.067	2.23	0.047	1.56	0.100	3.32	
10/14	4.21	3.04	72.2	0.378	8.98	0.078	1.85	0.060	1.43	0.253	6.01	0.5 gm. creatin
10/15	3.59	2.30	64.1	0.288	8.03	0.057	1.59	0.059	1.31	0.127	3.54	
10/16	3.19	2.21	69.3	0.402	12.6	0.071	2.28	0.054	1.69	0.100	3.14	
10/17	3.12	2.16	69.2	0.411	13.2	0.073	2.34	0.053	1.69	0.099	3.17	
10/18	3.15	2.30	73.0	0.353	11.2	0.057	1.81	0.053	1.68	0.101	3.21	

CASE 8.—*Progressive pseudohypertrophic muscular dystrophy.*

B. McD., white, male, 22 years of age, weight 53 kg. The condition was first noted a year previous to entering the hospital. There was increasing weakness and the arms and shoulders were getting smaller. The patient's normal weight was 60 kg.

There was moderate lordosis and the trunk was tilted to the left. The neck muscles were normal as regards strength and motion. The shoulders were not winged. The biceps and triceps had a tendinous feel. The calf muscles had the firm consistency of pseudohypertrophy. The patient walked with a waddling gait, but was quite active.

The diet consisted of 70 gm. protein, 90 gm. fat and 250 gm. carbohydrate; the energy value was 2,000 calories. On days June 2 and June 3, 1920, the protein intake was raised to 95 gm.

TABLE 9.—URINE NITROGEN PARTITION (CASE 8)

Day	Total N	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N		Remarks
	Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
5/30	10.12	7.60	75.1	0.693	6.84	0.280	2.85	0.370	3.66	0.050	0.49	
5/31	9.08	7.26	80.3	0.619	6.86	0.217	2.41	0.396	4.39	0.027	0.29	
6/ 1	10.42	8.22	79.1	0.494	4.75	0.200	1.92	0.363	3.49	0.063	0.61	
6/ 2	13.16	11.21	85.2	0.686	5.21	0.234	1.78	0.390	2.96	0.058	0.44	Protein 95 gm.
6/ 3	14.20	11.94	84.1	0.661	4.66	0.228	1.61	0.399	2.81	0.078	0.55	Protein 95 gm.
6/ 8	7.81	6.34	81.1	0.608	7.78	0.212	2.71	0.375	4.80	0.051	0.77	
6/ 9	7.56	5.85	77.4	0.556	7.36	0.221	2.92	0.402	5.31	0.139	1.85	1 gm. creatin
6/10	7.73	6.40	82.8	0.601	7.78	0.238	3.08	0.428	5.50	0.000	0.00	

CASE 9.—*Progressive pseudohypertrophic muscular dystrophy* (juvenile form.)

O. Sm., white, male, 38 years of age, weight 50 kg. The condition was first noticed when the patient was 18 years old; enlargement of the calves and beginning atrophy of the muscles from the waist down were then noted.

There was general weakness, pronounced lordosis and enlarged calf muscles as compared with the remaining musculature. The trunk, shoulder and arm muscles were small.

The patient was transferred to the metabolism unit May 17, 1920. He was placed on a diet of 79 gm. protein, 100 gm. fat and 220 gm. carbohydrate, and equivalent to 2,172 calories. The metabolism was not sufficiently stabilized for a satisfactory creatin ingestion observation. (A part of the data obtained on this case will be used in another paper, and is not included here.)

TABLE 10.—URINE NITROGEN PARTITION (CASE 9)

Day	Total N	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N		Remarks
	Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
5/18	8.61	7.32	85.0	0.771	8.95	0.228	2.65	0.212	2.46	0.072	0.84	
5/19	6.68	5.54	83.5	0.546	8.23	0.176	2.63	0.180	2.71	0.176	2.65	1 gm. creatin
5/23	8.40	....	....	.....	....	.....	....	0.214	2.55	0.125	1.49	

CASE 10.—*Myasthenia gravis.*

Geo. S., white, male, 51 years of age, weight 80 kg. The patient was admitted Sept. 4, 1919, complaining of increasing weakness of the arms and legs over a five year period.

There was bilateral external ophthalmoplegia and bilateral ptosis. Sensation of all types was normal. There was no ataxia of the upper or lower extremities. Knee jerk and plantar flexion were equal on both sides. Faradic stimulation of the anterior tibial group of muscles gave a poor response. Intermittent faradism induced fatigue of the flexors of the forearm, but the myasthenic reaction failed for the finger flexors.

The patient was in the metabolism unit for the period September 30 to October 4 only. The diet then given consisted of 51 gm. protein, 90 gm. fat, and 300 gm. carbohydrate, or 2,275 calories. A nonmeat and nonsoup diet was given September 5, and a general diet on September 24.

TABLE 11.—URINE NITROGEN PARTITION (CASE 10)

Day	Total N, Gm.	Ammonia N Gm.	Ammonia N %	Uric Acid N Gm.	Uric Acid N %	Creatinin N Gm.	Creatinin N %	Creatin N Gm.	Creatin N %	Remarks
9/ 5	12.23	.....	....	0.112	0.92	0.543	4.44	0.000	0.00	Nonpurine diet
9/24	8.79	.....	....	0.199	2.26	0.579	6.58	0.000	0.00	General diet
10/ 1	6.14	0.422	6.87	0.101	1.64	0.564	9.18	0.000	0.00	
10/ 3	5.80	0.398	6.86	0.078	1.34	0.564	9.72	0.000	0.00	

CASE 11.—*Acute anterior poliomyelitis.*

L. W., white, male, 25 years of age, weight 63 kg. The patient entered the hospital Sept. 2, 1920, complaining of inability to walk without aid. The condition developed just previous to admission.

The arms were normal in strength with no tremor or ataxia. The legs were held in normal position in the bed, and the muscle tonus at rest was normal. The patient was unable to raise any part of the right leg; he flexed the left knee 50 per cent., but could not raise the foot. Faradic stimulation showed the least response over the right buttock and thigh. There was a 25 per cent. response on the right calf and a 5 per cent. response on the right anterior tibial group. Sensation was normal.

While in the metabolism unit, the patient was given 75 gm. protein and from 2,000 to 2,500 calories daily.

TABLE 12.—URINE NITROGEN PARTITION (CASE 11)

Day	Total N, Gm.	Urea N Gm.	Urea N %	Ammonia N Gm.	Ammonia N %	Uric Acid N Gm.	Uric Acid N %	Creatinin N Gm.	Creatinin N %	Creatin N Gm.	Creatin N %	Remarks
10/3	14.43	10.72	74.3	0.690	4.78	0.154	1.07	0.480	3.32	0.055	0.38	
10/4	12.68	9.13	72.3	0.667	5.28	0.134	1.06	0.478	3.78	0.074	0.58	
10/5	12.35	9.28	75.1	0.717	5.81	0.122	0.98	0.451	3.65	0.024	0.19	
10/6	12.05	9.46	78.5	0.616	5.11	0.139	1.15	0.436	3.62	0.259	2.15	1 gm. creatin
10/7	12.45	10.57	84.9	0.787	6.32	0.126	1.01	0.437	3.51	0.058	0.47	

CASE 12.—*Myositis ossificans; chronic endocarditis, mitral stenosis and cardiac decompensation.*

Geo. F., white, male, 26 years of age, weight 54 kg. The patient was admitted to this hospital April 13, 1920. The duration of his illness was given as 18 months. It started with rheumatic symptoms.

The muscles of the trunk had a normal feel. The joints, except the hips and ankles were stiff and swollen, movements being restricted. The deltoid muscles seemed atrophied; the biceps and triceps were small. The muscles of the forearms had a bony feel. The thigh and calf muscles seemed hard and fibrous throughout.

The patient was transferred to the metabolism unit. He was placed on a nonpurin and noncreatin diet of 75 gm. protein, 72 gm. fat and 243 gm. carbohydrate, a total of 1,926 calories.

TABLE 13.—URINE NITROGEN PARTITION (CASE 12)

Day	Volume, C.c.	Specific Gravity	Total N, Gm.	Urea N		Ammonia N		Uric Acid N		Creatinin N		Creatin N	
				Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%
4/17	575	1.026	8.45	6.51	77.0	0.488	5.77	0.308	3.58	0.289	3.41	0.000	0.00
4/18	600	1.030	8.99	7.30	80.1	0.567	5.25	0.385	4.28	0.283	3.15	0.000	0.00
4/19	700	1.029	9.41	7.27	77.2	0.599	6.37	0.302	3.21	0.283	3.01	0.000	0.00
Balance period April 20-24 inc.													
Average per day....			9.62	....	....	.....	....	0.332	3.45	0.283	2.94		

	N Balance per Day, Gm.	Ca Balance for Period, Gm.	Mg Balance for Period, Gm.
Food	12.97	5.838	2.147
Urine	9.62	0.105	0.197
Stools	1.02	4.597	1.489
Total	10.69	4.702	1.686
Balance	+2.28	+1.136	+0.461

CASE 13.—*Progressive pseudohypertrophic muscular dystrophy.*

C. O., white, male, 10 years of age, weight 25 kg. The patient was referred to the medical service June 15, 1921.

The patient presented the characteristic picture of progressive pseudohypertrophic muscular dystrophy. There was lordosis and the patient walked with a waddling gait. When placed in a lying position on the floor and instructed to arise, he rolled on the side and pushed himself to a sitting position, but could not get up. He would stand with his feet widely apart in the characteristic lordotic position. The calf muscles were markedly hypertrophied.

TABLE 14.—URINE NITROGEN PARTITION (CASE 13)

Day	Total N, Gm.	Creatinin N		Creatin N		Remarks
		Gm.	%	Gm.	%	
6/15	3.68	0.056	1.52	0.078	2.12	
6/16	4.30	0.055	1.28	0.098	2.28	
6/17	4.55	0.057	1.25	0.081	1.78	
6/18	4.13	0.065	1.57	0.169	4.09	0.5 gm. creatin by mouth

The diet given consisted of 46 gm. protein, 70 gm. fat and 175 gm. carbohydrate, the total calories being 1,564.

THE NITROGEN REQUIREMENT FOR MAINTENANCE IN DIABETES MELLITUS*

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The general acceptance of the principle of restriction of the total caloric intake in the dietetic management of diabetes mellitus in contrast to the older principle of overfeeding has increased the importance of an accurate knowledge of the minimum amount of protein that will maintain nitrogenous equilibrium in the diabetic patient. The ultimate effect of long continued gradual loss of body nitrogen is not known, but it seems probable that such a condition is very undesirable. The subject whose nitrogen excretion is constantly higher than his nitrogen ingestion is certainly suffering for want of one of the most important of the tissue repairing elements, and a diet so arranged as to induce this negative balance, even though not lethal, must produce a severe grade of inanition.

The following experiments were undertaken in an effort to determine the minimum protein ingestion that will safely maintain nitrogen balance in patients with diabetes mellitus.

1. The usual method of determining the state of the nitrogen equilibrium was followed, namely, the balancing of the nitrogen in the food against the nitrogen in the urine and stools. Because of the difficulties in the way of collecting specimens from women, male patients were used. Their ages vary from 18 to 80 years. The severity of the disease also varied, as can be seen from the protocols, but over half were of the more severe types. In general, we chose the more intelligent patients as the ones most likely to cooperate with us by strict adherence to diet and in the collection of specimens, and care was taken to impress each of them with the importance of this cooperation.

The diets were arranged by an expert dietitian, and their delivery to the patients was carefully supervised by an unusually competent nurse. Copies of the diet lists were delivered to us daily, and were frequently checked against the ward reports. Uneaten portions were measured and deducted. The nitrogen content was determined by dividing the protein by 6.25, and the protein was estimated by use of

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Atwater and Bryant's food tables.[1] The heat value of 1 gm. fat was considered 9 calories and of 1 gm. protein or carbohydrate as 4 calories.

The nitrogen determinations on the stools, and on the urines of about half the cases were made by the Kjeldahl method, and on the remaining urines by the Folin micro-Kjeldahl method, after the two methods had been checked against each other. In some cases the quantitative nitrogen determinations were made daily; in the others aliquot parts of the acidified daily specimens were used. The stools were collected for several days, and their nitrogen content divided equally among the days during which they were passed. In a few cases, where nitrogen determinations on the stool are not available, the nitrogen excreted by this route has been estimated as 0.75 gm. daily. Since the nitrogen of the stool is only in small part derived from the unresorbed products of protein digestion, and since it is not directly dependent for its quantity on the food nitrogen, this is thought more accurate than the estimation of Mosenthal and Harrop[2] that 10 per cent. of the ingested nitrogen is excreted in the stool. Rieder[3] found a fecal excretion of 0.54, 0.87 and 0.78 gm. nitrogen daily from a man fed on a protein-free diet. The average fecal nitrogen of those cases in our series who were in balance on small amounts of ingested nitrogen, and who were not undergoing active catharsis was about 0.77 gm. daily.

In most cases, the nitrogen studies were incidental to the treatment, and in only a few was an effort made to find the lowest level at which nitrogen balance could be established. It is probable that had such an effort been made it would have given us lower figures for some of the patients. The treatment used was the low protein, high fat, low carbohydrate diets previously described by Newburgh and Marsh.[4] These diets were arranged with the intention of satisfying the caloric needs.

REPORT OF CASES

CASE 1 (19-293).—Patient was an American school teacher, aged 56, who entered the hospital, June 9, 1919, complaining of weakness. There was no history of diabetes in the family. The symptoms appeared five years before, with polyuria, polyphagia and polydipsia. There had been gradually increasing weakness, with obstinate constipation and mental depression. Nothing of

1. Atwater and Bryant: The Chemical Composition of American Food Materials, U. S. Dept. Agriculture, Bull. No. 28, 1906.

2. Mosenthal, H. O., and Harrop, G. A.: The Comparative Food Value of Protein, Fat and Alcohol in Diabetes Mellitus as Measured by the Nitrogen Equilibrium, Tr. Assn. Am. Phys. **33**:302, 1918; also Arch. Int. Med. **22**:750 (Nov.) 1918.

3. Rieder, H.: Bestimmung der Menge des im Kothe befindlichen, nicht von der Nahrung herrührenden Stickstoffes, Ztschr. f. Biol., N. F. **2**:378, 1884.

4. Newburgh, L. H., and Marsh, P. L.: The Use of a High Fat Diet in the Treatment of Diabetes Mellitus, Arch. Int. Med. **26**:647 (Dec.) 1920.

importance was found on physical examination. His blood sugar was 0.55 per cent., and his urine contained 50 gm. glucose per 1,000 c.c.

On a diet containing 16 gm. protein, 100 gm. fat and 10 gm. carbohydrate, with a total of about 1,000 calories, his urine became free of sugar on the fourth day, his ferric chlorid reaction became negative on the fifth day and his blood sugar had fallen to 0.14 per cent. on the sixth day. On an oatmeal and butter diet, which was given him a few days later, and which contained 9 gm. protein, 155 gm. fat and 31 gm. carbohydrate, a total of 1,550 calories, his blood sugar rose to 0.23 per cent. and glycosuria returned. A day of starvation sufficed to clear his urine of sugar. The nitrogen determinations

TABLE 1.—PART OF RECORD OF CASE 1

	Food				Urine		Blood	Nitrogen					
Date 1919	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Glucose, Gm.	Diacetic	Sugar, per Cent.	Urine,* Gm.	Stool,† Gm.	In, Gm.	Out, Gm.	Balance, Gm.	Wt., Lbs.
7/1	16.0	97.4	9.1	975	0	+	....	5.74	0.50	2.56	6.24	—3.68	.....
2	16.4	101.5	6.3	1,005	0	0	....	5.74	0.50	2.62	6.24	—3.62	.....
3	16.6	96.8	11.3	980	0	0	....	5.74	0.50	2.66	6.24	—3.58	.....
4	16.6	99.3	9.5	1,000	0	0	....	5.74	0.50	2.66	6.24	—3.58	.....
5	15.3	93.1	10.7	940	0	0	....	5.74	0.50	2.45	6.24	—3.79	.....
6	15.5	95.7	9.9	965	0	++	....	5.74	0.50	2.48	6.24	—3.76	.....
7	17.3	100.5	10.3	1,015	0	0	....	5.74	0.50	2.77	6.24	—3.47	.....
8	17.1	98.8	14.3	970	0	0	0.08	5.74	0.50	2.74	6.24	—3.50	.....
9	17.1	98.8	14.3	970	0	0	....	5.74	0.50	2.74	6.24	—3.50	.....
	Patient away from hospital for two weeks but did not adhere to diet												
22	....	....	....	.....	+	0	0.25	....	....	....	....	.....	.....
23	16.3	97.4	9.7	960	0	0	....	6.14	0.73	2.61	6.87	—4.26	142.5
24	16.3	97.4	9.7	960	0	0	....	6.14	0.73	2.61	6.87	—4.26	.....
25	16.3	97.4	9.7	960	0	0	0.09	6.14	0.73	2.61	6.87	—4.26	.....
26	16.3	97.4	9.7	960	0	0	....	6.14	0.73	2.61	6.87	—4.26	.....
27	16.3	97.4	9.7	960	0	0	....	6.14	0.73	2.61	6.87	—4.26	.....
28	16.3	97.4	9.7	960	0	0	0.11	6.14	0.73	2.61	6.87	—4.26	.....
29	16.0	97.4	8.9	975	0	0	....	5.68	0.53	2.56	6.21	—3.65	.....
30	10.7	59.9	5.2	605	0	0	....	5.68	0.53	1.71	6.21	—4.50	.....
31	15.7	96.3	9.0	965	0	0	....	5.68	0.53	2.51	6.21	—3.70	.....
8/1	18.4	135.0	4.8	1,310	0	0	0.08	5.68	0.53	2.94	6.21	—3.27	141.5
2	17.5	125.4	6.5	1,225	0	0	....	5.68	0.53	2.80	6.21	—3.41	.....
3	17.5	125.4	6.5	1,225	0	0	....	5.68	0.53	2.80	6.21	—3.41	.....
4	22.2	156.8	8.2	1,575	0	0	0.10	5.28	0.44	5.15	5.72	—0.57	.....
5	33.8	157.0	8.0	1,580	0	0	....	5.28	0.44	5.41	5.72	—0.31	140
6	33.5	157.0	7.5	1,575	0	0	....	5.28	0.44	5.35	5.72	—0.37	.....
7	33.5	157.0	7.5	1,575	0	0	....	5.28	0.44	5.35	5.72	—0.37	.....
8	36.4	163.0	7.5	1,645	0	0	....	5.28	0.44	5.82	5.72	+0.10	.....
9	34.3	168.4	6.9	1,680	0	0	....	5.23	0.40	5.49	5.63	—0.14	.....
10	34.3	168.4	6.9	1,680	0	0	0.10	5.25	0.40	5.49	5.63	—0.14	.....
11	34.3	168.4	6.9	1,680	0	0	....	5.23	0.40	5.49	5.63	—0.14	.....
12	34.3	168.4	6.9	1,680	0	0	....	5.23	0.40	5.49	5.63	—0.14	140
13	34.3	168.4	6.9	1,680	0	0	....	5.23	0.40	5.49	5.63	—0.14	.....
14	34.3	168.4	6.9	1,680	0	0	....	5.23	0.40	5.49	5.63	—0.14	.....
15	34.3	168.4	6.9	1,680	0	0	....	5.23	0.40	5.49	5.63	—0.14	137
16	34.3	168.4	6.9	1,680	0	0	....	5.23	0.40	5.49	5.63	—0.14	.....
17	34.3	168.4	6.9	1,680	0	0	0.10	5.23	0.40	5.49	5.63	—0.14	138

* Daily average of each period obtained from aliquot parts of urines.
† Daily average of each period obtained from all stools.

were begun a week later. It will be seen from Table 1 that a diet containing 34 gm. protein and 1,680 calories, with only 7 gm. carbohydrate practically established nitrogen equilibrium. This represents 0.54 gm. protein and 26 calories per kilogram of body weight.

CASE 2 (19-306).—Patient was a very mild diabetic, an American, 66 years of age, attendant at a state hospital for the insane. His symptoms were few, beginning three years before with thirst and polyuria. He had been on no diet before entrance to the hospital, June 30, 1919, except that he avoided "sweets." Two days of a low caloric diet sufficed to render his urine sugar free, and his blood sugar was found to be normal on the tenth day. No difficulty was met in establishing nitrogen equilibrium with an intake of two-

thirds gram of protein and from 33 to 40 calories per kilogram of body weight. Part of his record is presented in Table 2.

Case 3 (19-391).—Patient was an American factory inspector, who entered the surgical clinic for a herniotomy, and to obtain treatment for an infected leg. There was no diabetes in the family, and the patient had been well until six or eight years ago, weighing about 215 pounds. During the past few years he had noticed that he drank unusually large quantities of water and that he urinated frequently and copiously. His weight gradually fell to about 135 pounds, but he felt well and worked every day. Three weeks before entrance he injured his right leg. The wound became infected, was drained, but healed very slowly, and at the time of entrance was still draining pus. Except for the emaciation and dry skin, nothing of importance was noted in the examination. Throughout his stay in the medical ward he was afebrile.

The data from his study are presented in Table 3. The nitrogen studies were started after his blood sugar had been brought to normal by a diet containing 16 gm. protein, 100 gm. fat, 10 gm. carbohydrate and about 1,000 calories. It will be noted that on this diet his nitrogen output was large,

TABLE 2.—Part of Record from Case 2

	Diet				Urine				Blood Sugar,	Nitrogen†				
Date 1919	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories.	Amount, C.c.	Glucose, Gm.	Diacetic	N,* Gm.	per Cent.	Stool, Gm.	In, Gm.	Out, Gm.	Balance, Gm.	Wt., Lbs.
7/23	16.3	97.4	9.7	980	1,610	0	0	4.19	0.14	0.60	2.61	4.79	−2.18	141
24	16.3	97.4	9.7	980	820	0	0	4.19	....	0.60	2.61	4.79	−2.18	...
25	36.2	219.2	11.4	2,165	600	0	0	4.19	....	0.60	5.79	4.79	+1.00	...
26	36.2	219.2	11.4	2,165	825	0	0	4.19	....	0.60	5.79	4.79	+1.00	...
27	36.2	219.2	11.4	2,165	710	0	0	4.19	....	0.60	5.79	4.79	+1.00	...
28	36.2	219.2	11.4	2,165	725	0	0	5.61	0.12	0.55	5.79	6.16	−0.37	...
29	35.8	219.1	10.6	2,155	1,255	0	0	5.61	....	0.55	5.79	6.16	−0.37	141
30	36.2	219.2	11.4	2,165	970	0	0	5.61	....	0.55	5.79	6.16	−0.37	...
31	36.2	219.2	11.4	2,165	925	0	0	5.61	....	0.55	5.79	6.16	−0.37	...
8/ 1	41.5	243.8	14.8	2,420	1,360	0	0	5.61	....	0.55	6.64	6.16	+0.48	...
2	41.5	243.8	14.8	2,420	1,130	0	0	5.61	....	0.55	6.64	6.16	+0.48	...
3	47.3	255.4	12.3	2,535	1,175	0	0	5.61	0.11	0.55	7.57	6.16	+1.41	...
4	45.8	222.6	13.2	2,240	900	0	0	4.80	....	1.28	7.33	6.08	+1.25	...
5	46.1	258.8	13.2	2,560	1,100	0	0	4.80	....	1.28	7.37	6.08	+1.29	143
6	33.7	234.7	13.2	2,300	1,000	0	0	4.80	....	1.28	5.39	6.08	−0.69	...
7	46.1	228.8	13.2	2,290	1,190	0	0	4.80	....	1.28	7.37	6.08	+1.29	...
8	46.1	228.8	13.2	2,290	1,475	0	0	4.80	0.10	1.28	7.37	6.08	+1.29	145

* Daily average of each period obtained from aliquot parts of urines.
† Daily average of each period obtained from all stools.

amounting to nearly 14 gm. daily. With the addition of moderate amounts of protein and large quantities of fat to his diet, the nitrogen elimination gradually decreased until it reached about 8 gm. a day. This very mild diabetic with a body weight of 60 kilograms did not establish nitrogenous equilibrium on 40 gm. protein, during the few days allowed. Two explanations may be offered: First, it may have been that not enough time was allowed; this factor will be discussed later; or, second, that there was an increased destruction of protein as a result of his chronic infection. Balance was readily established by a diet containing 0.90 gm. protein and 42 calories per kilogram of body weight.

Case 4 (19-444).—Patient was an American farmer, 18 years old, who entered the hospital Sept. 5, 1919, complaining of weakness and excessive thirst. On one occasion, at the age of 14, he vomited a large quantity of blood. He noticed his polyuria and thirst a year and a half before; this was associated with increasing weakness. A physician found sugar in his urine, and under treatment the patient remained sugar-free for four months. After this he returned to an ordinary diet, and his weakness gradually increased. His best weight had been 135 pounds, two years before, and his weight at entrance was 95 pounds. For a year he had had crop after crop of boils.

Examination showed an emaciated young man with several boils on his hands and one on the left temporal region. The tendon reflexes were obtained only on reinforcement. The blood sugar was 0.525 per cent.

On a diet containing 16 gm. protein, 100 gm. fat and 10 gm. carbohydrate, with a total of 1,000 calories, his blood sugar fell to 0.20; at this time he left the hospital without permission, and ate a large quantity of carbohydrate. It was not until September 22 that his urine became free from sugar, and on September 25 his blood sugar was 0.15 per cent. A diet containing 28 gm. protein and 1,600 calories, representing 0.67 gm. protein and 38 calories per kilogram of body weight was found to establish nitrogen balance. Data from his case are presented in Table 4.

CASE 5 (19-537).—Patient, an American mailcarrier, 21 years of age, entered the hospital, Oct. 22, 1919, complaining of loss of strength. He had always been in excellent health until the onset of his diabetes a year before. His

TABLE 3.—PART OF RECORD FROM CASE 3

	Food				Urine			Blood	Nitrogen					
Date 1919	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Amount, C.c.	Glucose, Gm.	Diacetic	Sugar, per Cent.	Urine,* Gm.	Stool,† Gm.	In, Gm.	Out, Gm.	Balance, Gm.	Wt., Lbs.
8/21	16.3	97.4	9.7	970	1,775	0	0	0.08	....	....	....	....	.....	134
22	16.3	97.4	9.7	970	2,272	0	0	0.00	....	....	....	....	.....	...
Average	16.3	97.4	9.7	970	.....	..	..	....	12.68	1.17	2.61	13.85	—11.24	
25	30.0	128.0	10.3	1,315	2,350	0	0	....	....	....	....	....	.....	...
26	29.6	144.0	9.5	1,450	2,400	0	0	....	....	....	....	....	.....	130
27	29.6	150.0	9.1	1,500	3,470	0	0	0.13	....	....	....	....	.....	...
28	30.1	128.0	10.7	1,315	4,825	0	0	....	....	....	....	....	.....	129
Average	29.8	138.0	9.9	1,400	.....	..	..	....	9.96	1.85	4.77	11.81	—7.04	
9/ 1	40.3	219.0	12.6	2,185	1,125	0	0	0.11	....	....	....	....	.....	...
2	40.6	234.0	13.4	2,320	1,660	0	0	....	....	....	....	....	.....	...
3	41.5	228.0	13.4	2,270	1,250	0	0	....	....	....	....	....	.....	128
Average	40.8	227.0	13.1	2,260	.....	..	..	....	7.19	1.23	6.53	8.42	—1.89	
4	54.1	240.0	13.4	2,430	1,830	0	0	0.10	....	....	....	....	.....	...
5	54.1	240.0	13.4	2,430	1,825	0	0	....	....	....	....	....	.....	128
6	54.1	240.0	13.4	2,430	1,900	0	0	0.10	....	....	....	....	.....	...
7	54.1	240.0	13.4	2,430	1,135	0	0	....	....	....	....	....	.....	...
8	54.1	240.0	13.4	2,430	1,135	0	0	0.12	....	....	....	....	.....	129
Average	54.1	240.0	13.4	2,430	.....	..	..	....	7.01	1.11	8.66	8.12	+0.54	

* Daily average of each period obtained from aliquot parts of urines.
† Daily average of each period obtained from all stools.

only symptoms have been extreme weakness, a ravenous appetite, and a moderate polyuria. His weight fell from 165 to 119 pounds. Soon after the beginning of the diabetes he was placed by his physician on a diet consisting chiefly of milk, eggs, bran flour and fruit. The symptoms had become increasingly more severe. Examination showed a moderate emaciation, dry skin and absent knee reflexes.

On a diet containing 22 gm. protein, 110 gm. fat and 10 gm. carbohydrate, a total of 1,100 calories, he was sugar-free on the ninth day, though it was nearly a month before his blood sugar was found to be normal. It will be noted from the table that with a protein intake of 37.8 gm. and a total intake of 1,380 calories, he showed a negative balance of 2.11 and 2.83 gm. nitrogen, respectively, during the two periods in which the determinations were made, but that this fell to practical equilibrium when the total calories were raised to 1,650, though the protein and carbohydrate in the diet were unchanged. The diet contained 0.76 gm. protein and 36 calories per kilogram of body weight.

External circumstances made it necessary to discontinue the determinations before we were entirely finished. The large nitrogen content of the stool is explained by the fact that the patient took one-half ounce of magnesium sulphate daily.

TABLE 4.—PART OF RECORD FROM CASE 4

	Diet				Urine			Blood	Nitrogen					
Date 1919	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Amount, C.c.	Glucose, Gm.	Diacetic	Sugar, per Cent.	Urine,* Gm.	Stool,† Gm.	In, Gm.	Out, Gm.	Balance, Gm.	Wt., Lbs.
9/30	24.9	141.4	9.9	1,410	2,500	0	0	....	....	....	....	....	.....	85.5
10/ 1	24.9	141.4	9.9	1,410	2,500	0	0	....	....	....	....	....	.....	85
2	24.9	141.4	9.9	1,410	2,250	0	0	0.16	....	....	....	....	.....	84
3	24.9	141.4	9.9	1,410	2,750	0	0	....	....	....	....	....	.....	84.5
4	24.9	141.4	9.9	1,410	1,510	0	0	....	....	....	....	....	.....	85
5	24.9	141.4	9.9	1,410	2,650	0	0	....	....	....	....	....	.....	86
6	24.9	141.4	9.9	1,410	2,685	0	0	....	....	....	....	....	.....	86
7	24.9	141.4	9.9	1,410	1,300	0	0	0.15	....	....	....	....	.....	86.2
Average	24.9	141.4	9.9	1,410	.....	..	..	....	6.71	0.94	3.98	7.65	—3.67	
8	24.9	141.4	9.9	1,410	.....	0	0	....	....	....	....	....	.....	88
9	24.9	141.4	9.9	1,410	.....	0	0	....	....	....	....	....	.....	87
10	24.9	141.4	9.9	1,410	.....	0	0	0.13	....	....	....	....	.....	88
11	36.8	192.9	9.9	1,925	2,500	0	0	....	....	....	....	....	.....	88
12	36.8	192.9	9.9	1,925	2,585	0	0	0.13	....	....	....	....	.....	88.5
13	36.8	192.9	9.9	1,925	2,800	0	0	....	....	....	....	....	.....	88
14	36.8	192.9	9.9	1,925	2,050	0	0	....	....	....	....	....	.....	88
15	36.8	192.9	9.9	1,925	1,460	0	0	0.18	....	....	....	....	.....	88
16	36.8	192.9	9.9	1,925	2,000	0	0	....	....	....	....	....	.....	88
17	36.8	192.9	9.9	1,925	1,750	0	0	....	....	....	....	....	.....	87
Average	36.8	192.9	9.9	1,925	.....	..	..	....	5.38	0.98	5.89	6.31	—0.42	
18 to 21	36.8	192.9	9.9	1,925	.....	..	..	....	....	....	....	....	.....	88
22	36.8	192.9	9.9	1,925	1,065	0	0	....	....	....	....	....	.....	89.5
23	36.8	192.9	9.9	1,925	1,115	0	0	....	....	....	....	....	.....	90
24	36.8	192.9	9.9	1,925	1,420	0	0	0.15	....	....	....	....	.....	92.5
Average	36.8	192.9	9.9	1,925	.....	..	..	....	4.86	0.91	5.89	5.77	+0.12	
25	36.8	166.2	9.9	1,685	.....	0	0	....	....	....	....	....	.....	92.5
26	36.8	166.2	9.9	1,685	1,430	0	0	....	....	....	....	....	.....	93.5
27	36.8	166.2	9.9	1,685	1,535	0	0	....	....	....	....	....	.....	94
28	36.8	166.2	9.9	1,685	1,500	0	0	....	....	....	....	....	.....	94.5
29	36.8	166.2	9.9	1,685	2,000	0	0	....	....	....	....	....	.....	94.5
30	36.8	166.2	9.9	1,685	1,710	0	0	....	....	....	....	....	.....	94.5
31	36.8	166.2	9.9	1,685	2,470	0	0	....	....	....	....	....	.....	94.2
Average	36.8	166.2	9.9	1,685	.....	..	..	....	2.43	0.42	5.89	2.85	+3.04	
11-1	36.8	166.2	9.9	1,685	2,000	0	0	....	....	....	....	....	.....	94.5
2	36.8	166.2	9.9	1,685	2,420	0	0	....	....	....	....	....	.....	93
3	36.8	166.2	9.9	1,685	1,700	0	0	....	....	....	....	....	.....	83
Average	36.8	166.2	9.9	1,685	.....	..	..	....	2.97	0.45	5.89	3.42	+2.47	
4	28.1	162.8	9.9	1,615	1,850	0	0	....	....	....	....	....	.....	92.5
5	28.1	162.8	9.9	1,615	2,120	0	0	....	....	....	....	....	.....	92.5
6	28.1	162.8	9.9	1,615	1,800	0	0	....	....	....	....	....	.....	92
7	28.1	162.8	9.9	1,615	1,920	0	0	0.15	....	....	....	....	.....	91.5
Average	28.1	162.8	9.9	1,615	.....	..	..	....	2.97	0.45	4.49	3.42	+1.07	
8-10	28.1	162.8	9.9	1,615	.....	0	0	....	....	....	....	....	.....	92
11	28.1	162.8	9.9	1,615	2,235	0	0	....	....	....	....	....	.....	92.5
12	28.1	162.8	9.9	1,615	2,365	0	0	....	....	....	....	....	.....	92.2
13	28.1	162.8	9.9	1,615	2,425	0	0	....	....	....	....	....	.....	92.5
14	28.1	162.8	9.9	1,615	1,960	0	0	....	....	....	....	....	.....	92
Average	28.1	162.8	9.9	1,615	.....	..	..	....	1.21	1.15	4.49	2.36	+2.13	

* Daily average of each period obtained from aliquot parts of urines.
† Daily average of each period obtained from all stools.

CASE 6 (19-567).—Patient was a German coal dealer, 49 years of age, who entered the hospital, Nov. 11, 1919, complaining of weakness and polyuria. There was no history of diabetes in the family. He had always eaten heartily, but did not care for sweets and pastries. His symptoms first appeared eight

weeks ago, with increased thirst and polyuria, progressive weakness and loss of weight, the latter amounting to 30 pounds. A physician placed him on a diet consisting of eight slices of gluten bread, and half a dozen eggs daily, with all the meat he wanted. A second physician gave him nothing but milk and oatmeal. He noticed no improvement from either. There has been some numbness of the hands and feet, some constipation and no visual disturbances. Examination showed fair nourishment, with a dry skin. The tonsils were septic and the teeth in poor condition. There was moderate arteriosclerosis; the tendon reflexes were active.

TABLE 5.—PART OF RECORD FROM CASE 5

	Diet				Urine			Blood	Nitrogen					
Date 1919	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Amount, C.c.	Glucose, Gm.	Diacetic	Sugar, per Cent.	Urine,* Gm.	Stool,† Gm.	In, Gm.	Out, Gm.	Balance, Gm.	Wt., Lbs.
10/23	21.6	100.2	9.9	1,110	4,000	++++	+	0.30	....	....	....	....	.....	124
24	21.6	100.2	9.9	1,110	3,300	+++	+	....	....	....	....	....	.....	...
25	21.6	100.2	9.9	1,110	.....	+++	+	....	....	....	....	....	.....	...
26	21.6	100.2	9.9	1,110	1,800	++	+	....	....	....	....	....	.....	...
27	21.6	87.8	8.5	900	1,630	+	+	0.21	....	....	....	....	.....	119
28	15.5	42.1	9.5	480	1,530	++	+	....	....	....	....	....	.....	...
29	15.3	41.1	9.0	465	1,090	+	tr	....	....	....	....	....	.....	120
30	15.3	41.1	9.0	465	1,580	+	tr	....	....	....	....	....	.....	...
31	15.5	41.7	9.5	475	1,875	0	tr	...	....	....	....	....	.....	...
11/ 1	15.3	41.6	9.0	470	2,100	0	0	....	....	....	....	....	.....	122
2	15.5	41.7	9.5	475	2,430	0	0	....	....	....	....	....	.....	...
3	15.6	41.7	9.9	475	2,120	0	0	0.18	....	....	....	....	.....	120
Average	15.4	41.6	9.4	475	.....	..	..	....	8.50	0.84	2.47	9.34	—6.87	
4-5	37.4	133.7	8.0	1,380	2,450	0	0	....	....	....	....	....	.....	...
6	37.4	133.7	8.0	1,380	2,560	0	0	0.19	....	....	....	....	.....	116
7	37.4	133.7	8.0	1,380	2,825	0	0	....	....	....	....	....	.....	...
8	37.4	133.7	8.0	1,380	2,170	0	0	....	....	....	....	....	.....	114
9	37.4	133.7	8.0	1,380	2,500	0	0	....	....	....	....	....	.....	...
Average	37.4	133.7	8.0	1,380	.....	..	..	....	8.26	0.56	5.99	8.82	—2.83	
10-11	37.4	133.7	8.0	1,380	.....	0	0	....	....	....	....	....	.....	...
12	37.4	133.7	8.0	1,380	2,750	0	0	....	....	....	....	....	.....	113
13	37.4	133.7	8.0	1,380	3,560	0	0	....	....	....	....	....	.....	...
14	37.4	133.7	8.0	1,380	3,300	0	0	....	....	....	....	....	.....	...
Average	37.4	133.7	8.0	1,380	.....	..	..	....	6.75	1.35	5.99	8.10	—2.11	
15-18	37.4	133.7	8.0	1,380	.....	0	0	0.13	....	....	....	....	.....	113
19	37.6	147.6	8.0	1,510	.....	0	0	....	....	....	....	....	.....	...
20	37.6	165.6	8.2	1,675	.....	0	0	....	....	....	....	....	.....	116
21	37.6	165.3	8.3	1,675	.....	0	0	....	....	....	....	....	.....	...
22	37.6	165.6	8.3	1,675	3,670	0	0	....	....	....	....	....	.....	...
23	37.8	162.6	8.3	1,640	4,025	0	0	0.14	....	....	....	....	.....	118
24	37.6	163.6	8.2	1,650	4,090	0	0	....	....	....	....	....	.....	...
25	37.8	163.4	8.2	1,650	3,920	0	0	....	....	....	....	....	.....	...
26	37.8	163.6	8.2	1,650	3,955	0	0	....	....	....	....	....	.....	...
27	37.8	163.6	8.2	1,650	4,380	0	0	....	....	....	....	....	.....	120
Average	37.7	163.7	8.2	1,650	.....	..	..	....	5.11	1.51	6.66	6.62	—0.57	

* Daily average of each period obtained from aliquot parts of urines.
† Daily average of each period obtained from all stools.

On the fifth day of a diet containing 16 gm. protein, 100 gm. fat and 10 gm. carbohydrate, a total of 1,000 calories, his urine was free from sugar, and on the tenth day the ferric chlorid reaction became negative. He was given a diet containing 65 gm. protein and 2,065 calories, and was able to add 2.6 gm. nitrogen to his body daily for several days. After a few days, his nitrogen output increased, and he was practically in balance. Part of his record is presented in Table 6.

CASE 7 (20-18).—Patient, a locomotive fireman, 22 years of age, first entered the hospital, Jan. 16, 1920, complaining of excessive thirst and polyuria. There was no history of diabetes in the family. His symptoms were first noticed about six weeks before, and became gradually more severe, until he consulted a physician about January 1. The diagnosis of diabetes mellitus was made, and he was put on a diet of milk. His average weight was 130 pounds, and at admission it was 113 pounds. The physical examination showed nothing of importance.

On a diet containing 17 gm. protein, 100 gm. fat and 10 gm. carbohydrate, with a total of about 1,000 calories, his urine rapidly became sugar-free. His diet was increased gradually to 2,000 calories, with 40 gm. protein and 25 gm. carbohydrate, the remainder being fat. Through the summer, he reported to us at intervals, and his urine was always found to be sugar-free and his blood sugar within normal limits. He returned to the hospital in October, 1920, at

TABLE 6.—PART OF RECORD FROM CASE 6

	Diet				Urine			Blood Sugar.	Nitrogen					
Date 1919	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Amount, C.c.	Glucose, Gm.	Diacetic	per Cent.	Urine,* Gm.	Stool,† Gm.	In, Gm.	Out, Gm.	Balance, Gm.	Wt., Lbs.
11/22	15.9	97.2	9.9	980	1,800	0	0	0.12	....	....	....	....	.....	153
23	15.9	97.2	9.9	980	2,630	0	0	....	....	....	....	....	.....	...
24	15.9	97.2	9.9	980	2,250	0	0	....	....	....	....	....	.....	...
25	15.9	97.2	9.9	980	1,450	0	0	....	....	....	....	....	.....	...
26	15.9	97.2	9.9	980	1,550	0	0	....	....	....	....	....	.....	...
27	15.9	97.2	9.9	980	1,735	0	0	....	....	....	....	....	.....	...
Average	15.9	97.2	9.9	980	.....	..	..	....	6.02	0.53	2.54	6.55	—4.01	
11/28 to 12/ 2	65.0	197.0	9.9	2,065	.....	0	0	0.10	....	....	....	....	.....	...
3	65.0	197.0	9.9	2,065	2,450	0	0	0.07	....	....	....	....	.....	150
4	65.0	197.0	9.9	2,065	1,800	0	0	....	....	....	....	....	.....	...
5	65.0	197.0	9.9	2,065	1,830	0	0	....	....	....	....	....	.....	...
6	65.0	197.0	9.9	2,065	1,950	0	0	....	....	....	....	....	.....	156
7	65.0	197.0	9.9	2,065	2,440	0	0	0.10	....	....	....	....	.....	...
Average	65.0	197.0	9.9	2,065	.....	..	..	....	6.74	1.07	10.40	7.81	+2.59	
8-11	65.0	197.0	9.9	2,065	.....	0	0	....	....	....	....	....	.....	156
12	65.0	197.0	9.9	2,065	2,195	0	0	....	....	....	....	....	.....	156
13	65.0	197.0	9.9	2,065	2,535	0	0	....	....	....	....	....	.....	...
14	65.0	197.0	9.9	2,065	1,940	0	0	....	....	....	....	....	.....	155
15	65.0	197.0	9.9	2,065	1,700	0	0	....	....	....	....	....	.....	...
16	65.0	197.0	9.9	2,065	2,000	0	0	0.09	....	....	....	....	.....	...
17	65.0	197.0	9.9	2,065	2,265	0	0	....	....	....	....	....	.....	155
Average	65.0	197.0	9.9	2,065	.....	..	..	....	8.48	1.39	10.40	9.87	+0.53	

* Daily average of each period obtained from aliquot parts of urines.
† Daily average of each period obtained from all stools.

our request, so that further adjustment of his diet might be made. It was during this period that the studies in nitrogen balance were made, the data for which will be found in Table 7.

This patient was the subject of an interesting experiment that will be discussed later. Nitrogen balance was established on a diet containing 0.58 gm. protein and 21 calories per kilogram body weight.

CASE 8 (20-558).—Patient was a Syrian laborer, 36 years of age, who entered the hospital, July 25, 1920, complaining of excessive thirst and appetite, and polyuria. His symptoms were dated back eight months, during which period he had lost 35 pounds. He was a moderately severe diabetic who was able to tolerate 50 gm. carbohydrate and 30 gm. protein without glycosuria. His blood sugar was 0.37 per cent. at entrance, and his weight 162 pounds.

He was immediately placed on a diet consisting of 20 gm. protein, 90 gm. fat and 12 gm. carbohydrate, totaling about 950 calories. After three days,

his urinary sugar disappeared without the presence of a positive ferric chlorid test, and his blood sugar fell to 0.124 per cent. He remained on this diet until July 31. During the week following his carbohydrate intake was gradually increased each day, until August 7, he was eating 51.7 gm. without glycosuria. From August 8 to 12 he received 28 gm. protein, 115 gm. fat and 20 gm. carbohydrate with an energy value of about 1,225 calories. In the period from August 13 to 19 his average daily diet was 34 gm. protein, 165 gm. fat, 26 gm. carbohydrate and 1,725 calories. During this time his weight fell to 156 pounds. At this point the nitrogen determinations were started, the data for which are presented in Table 8. On the basis of a weight of 69 kg., nitrogen balance was established on 0.81 gm. protein and 33 calories per kilogram of body weight. There was a large positive balance at first which gradually fell, though there was a slight increase in the protein and caloric intake.

TABLE 7.—PART OF RECORD FROM CASE 7

	Diet				Urine			Blood Sugar.	Nitrogen					
Date 1920	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Amount, C.c.	Glucose, Gm.	Diacetic	per Cent.	Urine,* Gm.	Stool,† Gm.	In, Gm.	Out, Gm.	Balance, Gm.	Wt., Lbs.
11/12	11.1	45.4	9.2	490	.....	0	0	0.16	....	....	....	....	.....	...
13	21.5	80.4	14.6	870	.....	0	0	....	....	....	....	....	.....	128
14	20.6	87.6	14.6	930	.....	0	0	0.10	....	....	....	....	.....	...
15	105.7	115.9	15.0	1,885	.....	0	0	....	....	....	....	....	.....	...
16	106.5	96.0	15.0	1,710	1,350	0	0	....	9.58	1.42	31.44	11.00	+20.44	130
17	101.6	107.3	15.0	1,790	2,150	0	0	....	24.94	1.42	30.66	26.36	+4.30	...
18	107.9	104.5	14.9	1,790	2,450	0	0	....	14.68	1.42	31.66	16.10	+15.56	...
19	101.6	107.3	15.0	1,790	.....	0	0	0.12	....	....	30.66	....	.....	...
20	146.6	80.6	14.0	1,870	1,800	0	0	....	18.38	1.67	23.46	20.05	+3.41	130
21	82.1	121.8	23.9	1,320	2,100	0	0	....	29.76	1.67	5.13	31.43	—26.30	...
22	33.6	169.4	27.5	1,770	1,500	0	0	....	19.18	1.67	5.37	20.85	—15.48	...
23	34.3	174.7	29.9	1,830	950	0	0	....	7.76	1.67	5.49	9.43	—4.06	127
24	33.8	153.6	28.5	1,620	875	0	0	0.08	7.30	0.75‡	5.25	8.05	—3.80	...
25	28.7	116.8	20.8	1,250	1,225	0	0	....	9.37	0.75	4.59	10.12	—5.53	...
26	33.5	158.8	26.3	1,670	950	0	0	....	7.85	0.75	5.40	8.60	—3.20	...
27	33.0	89.7	21.9	1,030	1,350	0	0	....	2.35	0.75	5.37	3.10	+2.17	127
28	33.1	159.1	29.2	1,680	1,200	0	0	0.11	2.42	0.75	5.29	3.17	+2.12	...
29	34.8	167.1	25.0	1,745	1,250	0	0	....	3.05	0.75	5.57	3.80	+1.77	...
30	32.3	149.8	24.2	1,540	950	0	0	....	8.53	0.75	5.17	9.28	—4.11	128
31	32.9	160.3	25.9	1,760	1,150	0	0	....	8.33	0.75	5.27	9.08	—3.81	...
1	34.9	166.0	25.9	1,785	950	0	0	....	4.30	0.75	5.59	5.05	+0.54	...
2§	32.8	153.7	28.2	1,625	1,900	0	0	0.08	15.05	0.75	5.25	15.80	—10.55	...
3	53.5	211.6	37.5	2,270	1,200	0	0	....	7.06	0.75	8.56	8.71	—0.15	130
4	56.6	202.0	31.3	2,180	1,275	0	0	....	7.92	0.75	9.37	8.67	+0.70	...
5	58.8	213.4	39.4	2,315	1,250	0	0	....	9.12	0.75	9.60	9.87	—0.47	...

* Daily determinations. † Daily average of each period obtained from all stools.
‡ Estimated. § Acute follicular tonsillitis.

CASE 9 (20-677).—Patient was a German pattern maker, 63 years of age, who entered the hospital, Oct. 19, 1920, complaining of failing vision, polyuria, polyphagia and polydipsia. There was no family history of diabetes mellitus. The diabetic symptoms were first noticed about three years before, and though he was placed on a diet containing little carbohydrate, he continued to lose strength and weight, until on admission to the hospital he was hardly able to get about the house. His best weight was 150 pounds twenty years before. In the past two years he had lost 25 pounds, reaching his entrance weight of 111 pounds. Examination showed a moderate degree of emaciation. There was a mature cataract in the left eye and a beginning cataract in the right. The peripheral arteries were markedly sclerotic. There was some edema of the ankles and the tendon reflexes were normal.

On a diet containing 18 gm. protein, 90 gm. fat and 12 gm. carbohydrate, his urine became free from sugar on the twenty-fourth day, and four days later his blood sugar was 0.11 per cent. His diet was increased until he was

getting 34 gm. protein, 170 gm. fat and 23 gm. carbohydrate, a total of about 1,760 calories. December 3, he was transferred to the department of ophthalmology for operation, and was returned to the medical ward December 23 with a moderate glycosuria and a blood sugar of 0.17 per cent. Three days of a diet similar to that which he received immediately after admission sufficed to render his urine sugar-free, and his blood sugar fell to 0.14 per cent. His diet was again increased, and it was found that 55 gm. protein, 210 gm. fat and 35 gm. carbohydrate, with a total of about 2,250 calories, kept the sugar content of his blood between 0.19 and 0.20 per cent. though there was no glycosuria. His diet was accordingly reduced to 32 gm. protein, 160 gm. fat and 24 gm. carbohydrate, containing about 1,650 calories. On this diet

TABLE 8.—PART OF RECORD FROM CASE 8

	Diet				Urine		Nitrogen					
Date 1920	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Glucose, Gm.	Diacetic	Urine,* Gm.	Stool,† Gm.	In, Gm.	Out, Gm.	Balance, Gm.	Wt., Lbs.
9/20	33.6	181.3	25.8	1,870	0	0	....	....	....	....	....	156
21	34.7	151.1	26.4	1,605	0	0	....	....	....	....	....	...
22	33.5	174.7	26.2	1,810	0	0	....	....	....	....	....	...
23	31.0	200.5	26.7	2,115	0	0	....	....	....	....	....	...
Average	33.2	179.1	26.3	1,850	..	..	6.43	0.95	5.31	7.38	−2.07	
9/24	35.3	151.7	28.8	1,690	0	0	....	....	....	....	....	153
25	34.1	164.6	28.8	1,725	0	0	....	....	....	....	....	...
26	33.1	158.1	29.2	1,680	0	0	....	....	....	....	....	...
27	34.5	134.9	26.4	1,460	0	0	....	....	....	....	....	...
Average	34.2	153.1	27.8	1,625	..	..	6.70	1.14	5.47	7.84	−2.37	
9/28	54.8	206.9	29.8	2,240	0	0	....	....	....	....	....	152
29	54.0	207.6	27.0	2,220	0	0	....	....	....	....	....	...
30	57.6	209.0	29.3	2,270	0	0	....	....	....	....	....	...
Average	55.5	207.8	28.7	2,245	..	..	5.19	1.14	8.88	6.33	+2.55	
10/1	58.8	223.4	36.5	2,520	0	0	....	....	....	....	....	151
2	54.1	222.7	37.0	2,570	0	0	....	....	....	....	....	...
3	58.8	231.7	38.7	2,675	0	0	....	....	....	....	....	...
4	56.8	208.0	32.8	2,230	0	0	....	....	....	....	....	...
Average	57.4	221.4	36.2	2,370	..	..	7.06	1.08	9.18	8.16	+1.02	
10/5	54.3	223.7	33.6	2,365	0	0	....	....	....	....	....	151
6	56.4	202.7	37.7	2,350	0	0	....	....	....	....	....	...
7	65.5	211.3	35.3	2,505	0	0	....	....	....	....	....	...
8	59.8	249.2	39.2	2,640	0	0	....	....	....	....	....	...
Average	59.0	234.2	36.5	2,490	..	..	7.71	0.40	9.44	8.11	+1.33	

* Daily average of each period obtained from aliquot parts of urines.
† Daily average of each period obtained from all stools.

his blood sugar remained 0.15 per cent., and, as is shown in Table 9, he was in nitrogen balance. With a body weight of 50 kg., he was receiving on this diet about 0.64 gm. protein and about 33 calories per kilogram of body weight.

CASE 10 (20-615).—Patient, a very mild, elderly diabetic, returned to the hospital two years after he had been discharged on a moderately restricted diet. In the interval he had had no symptoms, except those of an associated chronic bronchitis, and he returned for examination. At entrance, his weight was 200 pounds, his age, 80 years, and his blood sugar 0.15 per cent. At no time during his stay did he have glycosuria or a positive ferric chlorid test on his urine. He was placed immediately on a diet containing about 1,500 calories of which about 34 gm. were protein. This was rapidly increased to a very liberal diet, as shown in Table 10.

CASE 11 (21-276).—Patient was an American farmer, 22 years old, who entered the hospital complaining of polyuria, weakness and loss of weight. A brother died of diabetes mellitus at the age of 17. His symptoms started seven months before and the diagnosis was made immediately. His diet was only moderately restricted, however, and he constantly lost weight and strength. His best weight had been 164 pounds just before the onset; his weight at admission was 127. Except for septic tonsils, his examination was negative. His blood plasma was creamy, and the total lipoids in the whole blood were

TABLE 9.—PART OF RECORD FROM CASE 9

	Diet				Urine			Blood Sugar,	Nitrogen					
Date	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Amount, C.c.	Glucose, Gm.	Diacetic	per Cent.	Urine,* Gm.	Stool,† Gm	In, Gm	Out, Gm.	Balance, Gm.	Wt., Lbs.
1/25	13.6	104.3	15.9	1,155	670	0	0	....	3.94	0.75	2.80	4.69	−2.19	...
26	28.7	124.5	19.2	1,810	680	0	0	0.15	4.08	0.75	4.59	4.83	−0.24	110
27	28.7	131.6	20.0	1,850	560	0	0	....	3.66	0.75	4.59	4.41	+0.18	...
28	32.8	147.3	24.5	1,555	670	0	0	....	3.98	0.75	5.25	4.73	+0.52	...
29	33.2	157.5	26.2	1,655	765	0	0	....	3.73	0.75	5.17	4.48	+0.69	109
30	34.7	185.4	26.7	1,915	.....	0	0	....	....	....	....	....	.....	...
31	34.7	159.1	28.2	1,685	735	0	0	....	3.53	0.75	5.55	4.27	+1.28	...
2/1	32.9	153.6	28.4	1,630	795	0	0	....	3.02	0.75	5.26	3.77	+1.49	...
2	32.6	172.8	29.6	1,800	745	0	0	0.15	3.17	0.75	5.25	3.92	+1.33	110
3	34.2	174.7	29.9	1,830	770	0	0	....	4.73	0.75	5.47	5.48	−0.01	...
4	34.7	190.1	25.9	1,955	.....	0	0	....	....	....	....	....	.....	...
5	34.6	170.5	19.8	1,750	1,255	0	0	....	4.70	0.75	5.54	5.45	+0.10	110
6	36.6	164.5	19.9	1,705	1,220	0	0	0.15	3.67	0.75	5.56	4.42	+1.44	...
7	33.3	167.3	18.4	1,710	1,020	0	0	....	3.40	0.75	5.17	4.15	+1.02	...
Average	31.8	157.4	23.8	1,640	.....	..	..	....	4.12	0.75	5.09	4.87	+0.22	

* Daily determinations. † Estimated

TABLE 10.—PART OF RECORD FROM CASE 10

	Diet				Urine		Nitrogen					
Date 1920	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Glucose, Gm.	Diacetic	Urine,* Gm.	Stool,† Gm.	In, Gm.	Out, Gm.	Balance, Gm.	Wt., Lbs.
9/26	24.1	164.6	28.8	1,735	0	0	....	....	....	....	....	200
27	33.1	159.1	29.2	1,680	0	0	....	....	....	....	....	198
28	34.5	135.0	26.4	1,460	0	0	....	....	....	....	....	197
29	33.8	111.1	29.3	1,255	0	0	....	....	....	....	....	199
30	34.1	143.0	26.3	1,530	0	0	....	....	....	....	....	200
Average	33.9	139.0	27.8	1,500	..	..	6.06	0.68	5.42	6.74	−1.32	
10/1	28.4	173.8	22.4	1,765	0	0	....	....	....	....	....	199
2	55.0	223.4	36.5	2,390	0	0	....	....	....	....	....	200
3	54.8	227.7	37.0	2,300	0	0	....	....	....	....	....	199
4	64.8	236.4	38.7	2,540	0	0	....	....	....	....	....	199
Average	51.4	214.1	33.9	2,200	..	..	3.83	1.17	8.22	5.00	+3.22	

* Daily average of each period obtained from aliquot parts of urines.
† Daily average of each period obtained from all stools.

found to be between 8 and 9 per cent. on several examinations immediately after admission to the ward. Part of the data of this case are presented in Table 11. He was established in nitrogen balance on a diet containing 0.74 gm. protein and about 37 calories per kilogram of body weight.

CASE 12 (21-678).—Patient was an American clerk, 18 years old, who entered the hospital March 24, 1921, complaining of weakness. There was no family history of diabetes. His symptoms began with polyuria, polydipsia, polyphagia, and progressive weakness, and his weight fell from 135 to 95 pounds. Treatment had been erratic, though at times his diet was restricted to green vegetables. Twelve days before entrance starvation was started, lasting

seven days; during the next five days he received green vegetables and a few eggs. For three months he had numbness and tingling of his hands and toes and there have been a few boils. The physical examination showed nothing of importance. Nitrogen balance was established on a diet containing 30 gm. protein, 180 gm. fat and 15 gm. carbohydrate, allowing him 0.71 gm. of protein and 43 calories per kilogram of body weight. The data are presented in Table 12.

TABLE 11.—PART OF RECORD FROM CASE 11
(DAILY AVERAGES FOR EACH PERIOD)

	Diet					Urine			Blood			Stool	Nitrogen		
Dates	No. of Days	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Glucose, Gm.	Diacetic	N, Gm.	Sugar, per Cent.	CO_2	Fat, per Cent.	N, Gm.	Wt., Lbs.	In, Gm.	Out, Gm.	Bal., Gm.
2/ 8 to 2/16	9	20.0	90.0	14.0	950	24.7 to 0	++++ to 0	....	0.26	61.4	8.50	....	126	....	....	.....
2/17 to 2/21	5	20.8	82.8	13.7	885	0	0	9.72	0.12	56.6	....	....	121	3.23	....	.....
2/22 to 2/24	3	40.1	154.4	29.2	1,630	0	0	7.37	....	46.8	7.00	....	122	6.42	....	.....
2/25 to 3/1	5	40.2	152.6	29.5	1,615	0	0	7.84	0.13	62.6	7.90	....	122	6.43	....	.....
3/ 2 to 3/7	6	40.8	152.1	29.6	1,615	0	0	8.96	0.12	58.9	6.70	....	119	6.53	....	.....
3/ 8 to 3/12	5	40.0	180.3	29.4	1,865	0	0	6.75	....	....	6.25	....	124	6.40	....	.....
3/13 to 3/17	5	40.0	179.4	29.6	1,855	0	0	5.65	....	65.2	4.32	....	126	6.40	....	.....
3/18 to 3/20	3	40.5	200.3	25.0	2,065	0	0	5.28	....	59.8	3.12	1.39	125	6.48	6.67	—0.19
3/21 to 3/29	9	40.9	200.9	25.0	2,070	0	0	6.12	0.08	65.3	2.89	0.98	121	6.54	7.10	—0.56
3/30 to 4/4	6	40.6	200.2	25.0	2,065	0	0	5.33	0.10	60.7	2.71	0.95	121	6.50	6.48	+0.02
4/ 5 to 4/8	4	43.1	229.1	25.6	2,340	0	0	4.01	....	61.7	2.54	0.95	121	6.90	4.96	+1.94

TABLE 12.—PART OF RECORD FROM CASE 12

	Diet				Urine				Blood			Stool		Remarks		
Date 1921	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Amt., C.c.	Glucose, Gm.	Diacetic	N,* Gm.	Sugar, per Cent.	CO_2	Fat, per Cent.	N,† Gm.	Wt., Lbs.	N In, Gm.	N Out, Gm.	N Bal., Gm.
3/24	....	.....	....	.....	.....	+++	+	....	0.330	61.4	2.63	....	93.0	....	....	.....
25	21.7	99.4	14.8	905	1,065	++	tr	....	.....	....	....	....	....	....	....	.....
26	29.1	129.1	21.1	1,320	2,000	0	0	....	.....	....	....	....	89.5	....	....	.....
27	19.1	95.4	14.2	900	2,225	0	0	....	.....	....	....	....	....	....	....	.....
28	21.2	85.9	13.4	910	2,900	0	0	....	0.234	61.7	2.21	....	....	....	....	.....
29	20.2	92.4	14.6	900	2,925	0	0	....	.....	....	....	....	....	....	....	.....
30	30.0	147.1	14.2	1,500	3,280	0	0	6.21	.....	....	....	0.75	91.5	4.80	6.96	—2.16
31	31.7	151.9	15.5	1,535	4,490	0	0	6.21	.....	....	....	0.75	....	5.07	6.96	—1.89
4/ 1	29.9	149.4	14.8	1,525	2,310	0	0	4.62	.....	....	....	0.75	....	4.78	5.37	—0.59
2	30.2	149.3	14.9	1,525	3,435	0	0	4.62	.....	....	....	0.75	91.0	4.83	5.37	—0.54
3	28.8	152.4	14.8	1,545	1,760	0	0	4.62	.....	....	....	0.75	....	4.61	5.37	—0.76
4	30.3	152.0	14.9	1,550	2,220	0	0	4.62	0.164	63.6	1.44	0.75	....	4.85	5.37	—0.52
5	31.1	180.7	14.2	1,800	3,220	0	0	4.11	.....	....	....	0.75	....	4.98	4.86	+0.12
6	30.0	179.3	14.2	1,785	2,260	0	0	4.11	.....	....	....	0.75	92.0	4.80	4.86	—0.06
7	29.1	178.2	15.0	1,795	2,410	0	0	4.11	.....	....	....	0.75	....	4.67	4.86	—0.19
8	29.7	180.2	15.3	1,800	3,080	0	0	4.11	0.164	61.7	1.40	0.75	....	4.75	4.86	—0.11

* Daily average of each period obtained from aliquot parts of urines.
† Estimated.

2. Recently Sherman [5] has added to his own careful studies of the protein requirement for maintenance of nitrogen balance in normal men a complete collection of data obtained from the literature, 109

5. Sherman, H. C.: Protein Requirement of Maintenance in Man and the Nutritive Efficiency of Bread Protein, J. Biol. Chem. **41**:97, 1920.

experiments in all. An average of all minimum daily protein intakes on which nitrogen balance was established gave 0.635 gm. protein per kilogram of body weight. If the seventy-six determinations showing the least variation are averaged, a lower figure, 0.58 gm., is obtained. He points out that the more recent data are, as a result of more accurate methods and a better understanding of the problem, somewhat lower than those obtained by the earlier observers, and he himself was able to maintain several subjects in nitrogen balance on 0.5 or even 0.45 gm. protein per kilogram of body weight per day. The experiments of Hindhede,[6] Chittenden [7] and others are too well known to require comment. It is an established fact that nitrogen balance may be maintained on less than 0.66 gm. protein per kilogram of body weight per day, provided certain other conditions are satisfied.

The conditions necessary for the establishment of nitrogen balance at this low level are several. Chief among them is the presence of sufficient total calories in the ingested food; there must be enough fat or carbohydrate in the diet to supply all the body needs for heat and energy, so that the protein may be used only for restoring body tissue. The protein-sparing qualities of carbohydrate and fat were discovered by some of the earliest students of metabolism, and it is well known that carbohydrate is the more efficient of the two in sparing protein, though in a mixed diet fat may replace carbohydrate in isodynamic quantities. In spite of this difference in the effectiveness of the two foodstuffs, the ability of fat to spare protein cannot be doubted. For example, Thomas, quoted by Lusk,[8] "could not maintain nitrogen equilibrium when twice the amount of the fasting nitrogen elimination was given to man in the form of meat alone, but was able to accomplish this when meat to the extent of that destroyed in the fasting was administered with fat." It is important, then, to remember that if nitrogen balance is to be maintained on a low protein intake the total calories in the food must be sufficient to supply metabolic needs.

While a partial replacement by fat of carbohydrate in a low protein diet will not affect the protein metabolism, complete withdrawal of carbohydrate and substitution of fat will not permit the establishment of nitrogen balance at low levels. Fat alone will not decrease the amount of nitrogen found in the urine of a fasting animal.[9] It is generally believed that fat in a low protein diet loses part of its effectiveness when the carbohydrate calories fall below 10 per cent. of the total calories. Thus Zeller [10] found that a man receiving little nitrogen

6. Hindhede, M.: Skand. Arch. Physiol. **30**:97, 1913; **31**:259, 1914.
7. Chittenden, R. H.: Physiological Economy in Nutrition, 1904; Nutrition of Man, 1907.
8. Lusk, G.: Science of Nutrition, Philadelphia, 1919, p. 254.
9. Voit: Physiologie des Stoffwechsels und der Ernährung, 1881, p. 128; Bartman: Ztschr. f. Biol. **58**:375, 1912.
10. Zeller: Arch. f. Physiol., 1914, p. 213.

in his food and varying amounts of carbohydrate and fat showed little variations in his nitrogen excretion until the carbohydrate gave less than 10 per cent. of the total calories.

It was stated that fat alone will not decrease the amount of nitrogen eliminated during starvation. It is also of great interest in connection with diabetes to note that in an animal still possessing body fat, fat in the diet does not bring about any change in the amount of fat metabolized. Voit,[9] for example, gave 100 gm. fat to a dog, which in starvation burned 96 gm. fat, and found that it burned 97 gm. In other words, the same amount of fat was burned whether it was derived from the body or from the diet. The amount of fat stored in the body has, however, a direct influence on the amount of protein metabolized during starvation. Lean animals die of starvation sooner than fat animals, and as starvation progresses and the relative quantity of fat and protein in the organism decreases the output of urinary nitrogen

TABLE 13.—EFFECT OF PREVIOUS DIET ON NITROGEN EXCRETION
(C. VOIT)

Amount of meat in previous diet...	2,500 gm.	1,500 gm.	Mixed diet poor in N
	Amount of Protein Used as Determined by Urine N		
First fast day	175	77	40
Second fast day	72	54	33
Third fast day	53	46	30
Fourth fast day	50	53	36
Fifth fast day	36	43	35
Sixth fast day	39	37	36

increases. Folin and Denis [11] found that the protein metabolism in fasting was low in people in whom ample fat was present. On the other hand, if the fat be supplied in the diet, there is no difference in the protein metabolism of a lean subject and that of a fat one. The total metabolism of an obese man is the same in proportion to his body surface as in a lean man. These facts are of practical value in the arrangement of diets for diabetics of different degrees of nourishment, and must not be ignored in the study of their nitrogen requirements.

A very marked effect of the previous diet is noted during the first few days of the study of nitrogen balance. This is shown very nicely in the experiment by C. Voit, tabulated by Magnus-Levy,[12] the data from which are shown in Table 13. The diets containing the amounts of meat indicated had been continued for several days before each experiment.

It will be noted that it is not until the sixth day that the nitrogen outputs reach a common level. This may be considered as due to the fact that excess of protein in the tissues or in the blood stimulates

11. Folin and Denis: J. Biol. Chem. **21**:183, 1915.
12. Magnus-Levy, A.: Von Noorden's Handbuch der Pathologie des Stoffwechsels, 1906, p. 312.

protein metabolism. The experiment is of great importance in emphasizing the fact that studies in nitrogen balance made during the first few days following a change in diet are of no value; the organism requires some time for its readjustment to the new dietetic regime.

On the other hand, Rubner, quoted by Lusk,[8] states that the "greater the impoverishment of the protein supply in an animal fed with fat, the more powerful is the protective effect of small quantities of ingested protein over the loss of body protein. Also the retention of protein depends on the protein content of the dog as well as on the quantity of protein ingested." This is illustrated in Table 14.

"It is evident from this that of the same diet of protein more will be retained when the nitrogen content of the dog is low than when it is high; and also that a small protein intake may cause the same retention of nitrogen as a large protein intake, if in the first instance there be a relative impoverishment of the protein content of the animal."

TABLE 14.—PROTECTIVE EFFECT OF SMALL QUANTITIES OF PROTEIN WHEN BODY PROTEIN IS IMPOVERISHED
(RUBNER)

Total N Content of Dog	N in Terms of 100 N in Dog	
	In Food	To Body
318.8	5.25	1.65
354.7	5.57	1.02
310.6	6.73	2.64
363.7	12.79	2.62

It has been stated that in order to maintain nitrogen balance on a diet with a small protein content, the total caloric requirement of the subject must be satisfied. This requirement is not represented by the rate of basal metabolism. The caloric needs of the fasting, resting subject are not the same as those of the same subject after the ingestion of food or in the performance of even the smallest amount of work. A certain amount of energy is used in the metabolism of the food, and this "specific dynamic action" is different for each of the three major foodstuffs. For protein the increased heat production is especially high, amounting to from 25 to 35 per cent. of the ingested calories. In the case of fat the figure is about 12 per cent.; for carbohydrate much less, about 6 per cent. This factor must enter into our calculations of the total daily requirement, and if the diet contains an excess of protein, the amount of food necessary to supply the caloric needs of the body, and hence to maintain nitrogen equilibrium, is considerably greater than when fat and carbohydrate furnish the major part of the calories.

The amount of work done by the subject obviously influences his caloric needs. A man whose resting requirements are satisfied by 1,500 calories daily may burn 9,000 calories in a bicycle race. It is evident that this fact must be considered in the formation of a low protein

diet that will maintain nitrogen balance. On the other hand, there is abundant evidence to show that work does not increase the rate of protein metabolism when the energy is supplied from other foodstuffs. The experiment by Shaffer [13] presented in Table 15 may be cited as an example; during the first period he was at rest in bed; during the second he was doing laboratory work, and during the third, laboratory work plus a ten-mile walk daily; the periods were six, five and four days respectively.

The other end-products of protein catabolism showed a similar constancy, and he concluded from this that muscular activity had no effect on protein metabolism. This fact is important because we may arrange the protein content of a diet without regard to the amount of work that the patient will do. If he is in nitrogen balance at rest, the calories required for energy for work may be added as fat or carbohydrate. Furthermore, it has been shown that there is no difference in value of fat and carbohydrate as a fuel for mechanical work.[14]

TABLE 15.—Effect of Work on Protein Metabolism (Shaffer)

Period	Food		Urine
	N	Calories	N
1	5.9	2,300	4.77
2	6.0	3,000	4.40
3	5.9	3,200	3.94

In the formation of diets the age of the subject must receive consideration. The total caloric requirement of children is much greater in proportion to their size than is that of adults, and this requirement declines as the subject becomes older. Furthermore, beside the "repair quota" of protein needed to replace that lost in the wear and tear of tissue, children require a "growth quota." While, as far as we know, there is no record of a careful determination of the minimum protein intake that will supply the normal growing child with the needed nitrogen, it must be considerably higher than that required by adults.

Sex is of no importance in this connection. Some of the studies discussed by Sherman [5] had for their subjects women. Since women have a somewhat lower metabolic rate than men, a diet that is sufficient to supply the needs of a man will certainly supply those of a woman of the same size. There is no change in the oxidation processes during menstruation,[15] and the amount of nitrogen lost is evidently

13. Shaffer, P. A.: Diminished Muscular Activity and Protein Metabolism, Am. J. Physiol. **22**:445, 1908.

14. Zuntz: Arch. f. d. ges Physiol. **83**:557, 1900.

15. Gephart, A. B., and Du Bois, E. F.: Basal Metabolism of Normal Adults, Arch. Int. Med. **17**:907 (June) 1916; Blunt, K., and Dye, M.: Basal Metabolism of Normal Women, J. Biol. Chem. **47**:69, 1921.

small. The pregnant woman requires an extra quota of nitrogen and extra calories during the gestation period in order to supply the embryo; as the weight of the child at birth is only 5 or 6 per cent. of that of the mother, the extra ration need not be very great.

The weight of the subject is of importance in giving us a basis on which we may calculate his nitrogen requirements and, roughly, his total diet. Gain and loss of weight during the periods of treatment when the diets are being changed mean little, as a rule, because such changes are very often due to changes in the water content of the body. In the normal subject, change from a carbohydrate diet to a fat or protein diet causes a loss of water [16] amounting to as much as a kilogram a day. Dehydrated subjects, on the other hand, may absorb and retain enormous quantities of water, with the resulting increase in body weight. This is seen not only in diabetes, but in other diseases, as pyloric obstruction. We therefore frequently see the apparent paradox of a patient who gains weight rapidly on a diet containing only 1,000

TABLE 16.—Effect of Ingested Water on Nitrogen Excretion (Abderhalden and Bloch)

	N Balance	N in Urine
Normal food	+1.36	18.2
Normal food plus 5 liters water	−2.19	21.75
Normal food	+1.47	18.09

calories daily. More than this, the more severe cases of diabetes show a marked tendency to the development of edema. Because of these facts, one is not entitled to draw conclusions as to the state of the patient's nutrition from changes in body weight. As pointed out before, the important consideration is the fat and protein content of the body.

A small increase in nitrogen elimination has usually been noted following the drinking of large quantities of water. Hawk,[17] for example, found that the ingestion of 4,500 c.c. water with an unchanged nitrogen content of the diet caused the urinary nitrogen to rise from 11.03 to 12.48 on the first day, and 11.82 on the second, with a fall of 10.91 on the succeeding day when no water was given. Alderhalden and Block [18] gave a subject on a fixed diet 5 liters of water with the results shown in Table 16.

It is probable that two factors explain this rise in nitrogen elimination; first, the water removes from the body any accumulation of the end-products of nitrogenous metabolism, and second, causes a true increase of the protein metabolism. This is of interest in the case of

16. Bischoff and Voit: Die Gesetze der Ernährung des Fleisch fressers, Leipsic, 1860; Benedict, Milner: U. S. Dept. Agric. Office, Exper. Stat. Bull. 175, 1907.

17. Hawk: Univ. Penn. Med. Bull., March, 1905.

18. Abderhalden and Bloch: Ztschr. f. Physiol. Chem. **53**:464, 1907.

a diabetic who drinks large quantities of water, either as a symptom of his untreated disease or during periods of very restricted diet when he attempts to relieve some of the pangs of hunger by filling his stomach.

There is also an irregular but important day to day variation in the nitrogen output that is independent of variations in fluid intake. These fluctuations are the result of lag in excretion, and in the long run they are compensatory. A nitrogen determination for a single day is an unsafe indication of the usual excretion; safety is in the average of several days.

Beside all these factors influencing the protein metabolism, there are a few manifestations of nondiabetic disease which may cause profound disturbances in the nitrogen balance. The great increase in the rate of total metabolism and especially of protein metabolism in hyperthyroidism is well known. In the diabetic, the most important cause of such disturbances is fever. The increase in nitrogen elimination during fever may be enormous. In a study of the metabolism in pneumonia, for example,[19] the daily loss in nitrogen on a diet adequate to protect a normal individual from loss may be from 20 to 25 gm., representing from 125 to 150 gm. protein. Of chief importance in the study of diabetes is tuberculosis, in which the destruction of protein, while smaller than in pneumonia, is continued over a much longer time.[20] Even during the afebrile periods there is some increase over normal in the protein destruction. Futhermore, in these infectious fevers, the total caloric requirement is greater than normal because of the increased heat production. The presence of such a fever must modify our diet in diabetes.

3. It is seen, then, that the normal subject may be maintained in nitrogen balance on less than 0.66 gm. protein per kilogram of body weight, provided the total caloric intake is sufficient to supply heat and energy. Certain fundamental laws governing protein metabolism have been discussed, and because of their importance are here restated.

In mixed diets carbohydrate and fat are equally efficient in sparing protein and of equal value as fuel for work. Carbohydrate may not be entirely replaced by fat, however. An animal having a supply of body fat will burn the same amount of fat, whether it is supplied in his diet or is used from his store. A good supply of body fat thus saves protein in the same way as ingested fat. More nitrogen is excreted during the days following a diet rich in protein than following one poor in protein. The increased heat elimination due to the metabolism of food

19. Wolf and Lambert: Protein Metabolism in Pneumonia, Arch. Int. Med. **5**:406 (March) 1910.

20. May: Ott's Chemische Pathologie der Tuberculose, Berlin, 1903, p. 335. McCann, W. S., and Barr, D. P.: The Metabolism in Tuberculosis, Arch. Int. Med. **26**:663 (Nov.) 1920.

has been pointed out, and the excessive "specific dynamic action" of protein has been emphasized. Work causes an increase in the total metabolism, but no increase in the protein metabolism provided the calories needed are supplied in other form. Children require more protein than adults, and the total requirement decreases as age advances. Sex is of no importance in studies of protein metabolism. There is a marked day to day fluctuation in nitrogen excretion, partially dependent on increased water intake. Changes in weight must be interpreted with caution, because they are often due to changes in the water content of the body. The infectious fevers cause a great increase in the amount of protein destruction.

The laws governing protein metabolism of normal subjects have been stated. The question then arises as to whether or not these facts apply equally to the diabetic. Is there any peculiar disturbance of his

TABLE 17.—PROTEIN SPARING QUALITIES OF FAT IN DIABETES MELLITUS (WEINTRAUD)

Date	Protein, Gm.	Fat, Gm.	N in Food, Gm.	N in Stool, Gm.	N in Urine, Gm.	N Balance, Gm.
9	113	273	18.19	0.9	16.49	+0.80
10	113	273	18.19	0.9	16.34	+0.95
11	113	273	18.19	0.9	16.88	+0.41
12	113	273	18.19	0.9	16.01	+1.28
13	113	273	18.19	0.9	14.00	+3.29
14	111	28.5	17.74	1.04	17.2	−0.5
15	111	28.5	17.74	1.04	21.51	−4.81
16	111	28.5	17.74	1.04	23.37	−6.67
17	113	273	18.19	1.52	19.29	−2.62
18	113	273	18.19	1.04	19.29	−2.72
19	113	275	18.01	1.52	19.61	−3.12
20	113	275	18.01	1.52	17.07	−0.58
21	113	273	18.19	1.31	15.54	+1.34
22	113	273	18.19	1.31	14.39	+2.49
23	113	273	18.19	1.31	14.2	+2.68
24	113	275	18.19	1.31	13.88	+3.00

protein metabolism that makes his nitrogen requirement higher than that of his normal brother? Is his protein metabolism affected to the same degree and by the same factors as is that of a healthy subject?

That the urine in diabetes may contain more nitrogen than that of any other disease has been known for a long time and the French even gave this finding a name, azoturia. Von Noorden,[21] however, pointed out that this is due to the large nitrogen content of the diabetic's diet, either because of his own tendency to replace with protein the carbohydrate calories lost in the urine, or because of the very high protein content of the contemporary diabetic diet.

Weintraud[22] demonstrated conclusively as long ago as 1893 that fat fed to the diabetic subject was very powerful in saving his protein. An example of his experiments is shown in Table 17.

21. Von Noorden, C.: Die Zuckerkrankheit, Berlin, 1907, p. 97.
22. Weintraud, E.: Stoffwechsel in Diabetes Mellitus, Cassell, 1893.

It will be noted (1) that a decrease in fat calories without change in the nitrogen in the food resulted in the immediate production of a negative nitrogen balance; (2) the return to the diet rich in fat left the patient in negative balance for the first four days of the regime; but (3) during the second four days he was able to add nitrogen to his body. Had the experiment begun on the fourteenth and ended on the twenty-first, we would have been led to the conclusion that the fat did not spare nitrogen; a similar conclusion would result from the discontinuance of the experiment on the twenty-second, with the average nitrogen output of the first six days following the change. The fallacy of drawing conclusions from observations on the days immediately following changes in diet is apparent. The author also made quantitative determinations of the fat in the stools, in an effort to show whether or not there was any difficulty in the absorbtion of large quantities of fat from the intestinal tract of diabetics. Three normal subjects excreted an average of 3.2 per cent. of 150 gm. of fat. Table 18 presents his results in cases of three grades of diabetes.

TABLE 18.—Fat Absorbed from High Fat Diets in Diabetes Mellitus (Weintraud)

Severity	Food Fat, Gm.	Stool Fat, Gm.	Fat Absorbed	
			Gm.	Per Cent.
Severe	45.94	7.41	38.53	83.87
	146.4	4.53	141.86	96.90
	272.04	3.31	268.73	98.78
Moderately severe	39.42	2.16	37.24	94.47
	147.17	2.52	144.65	98.28
	206.02	3.10	202.92	98.61
Mild	55.41	3.15	52.26	94.31
	236.11	4.35	231.76	98.15

This general relationship held in all his determinations, namely that the percentage of fat in the stools fell with increase in the fat intake, and all of his diabetics showed an average absorbtion of about 98 per cent. of the ingested fat when the latter was over 125 gm. daily.

Dunlop [23] doubted the value of fat in sparing protein in diabetes, as demonstrated by Weintraud [22] and quoted in support of his doubt the experiment of Karsëner [24] who brought himself into nitrogenous equilibrium on a diet of protein and carbohydrate, and found that he was no longer able to maintain this equilibrium when he replaced a large part of the carbohydrate with the caloric equivalent of fat. Dunlop fed a diabetic patient 4,660 c.c. of skimmed milk for two periods of three days each, and then added to the milk diet a daily ration of 170 c.c. of olive oil. The results are shown in Table 19.

23. Dunlop, J. C.: Dietetic Values of Fat in Diabetes, Edinburgh M. J. **42**:399, 1896.

24. Karsëner: Von Noorden's Beiträge z. Lehre v. Stoffwechsel, Heft 1.

Because the oil did not decrease the nitrogen in the urine, the author argues that it did not act as a nitrogen sparer. This is, of course, only in accord with the established fact that a subject cannot be forced to store nitrogen, and that nitrogen ingested in excess of the requirement will be excreted rather than stored; the experiments show nothing in regard to the protein sparing qualities of fat. The experiment of Karsëner merely confirms the greater efficiency of carbohydrate than fat in sparing protein.

The excessive nitrogen excretion of totally depancreatized dogs is well recognized, and may reach five times the normal amount.[25] Sometimes these dogs develop a rapid and fatal cachexia without glycosuria, indicating, it would seem to us, that the excessive nitrogenous metabolism in such depancreatized animals was not part of the diabetic state. Furthermore, numerous pancreatic operations on human beings have been reported in which there was greatly increased nitrogen excretion

TABLE 19.—The Effect of Adding Fat to the Diet of a Diabetic Already in Nitrogen Balance
(Dunlop)

Period	Food		Nitrogen Output		
	N.	Added Oil	Urine	Stool	N-Balance
1	24.8	...	19.41	0.39	+5.00
2	24.8	170	18.02	0.44	+6.34
3	24.8	...	24.16	0.38	+0.26
4	24.8	170	25.06	....	−0.26
Av. 1, 3	24.8	...	21.8	0.38	+2.62
Av. 2, 4	24.8	170	21.54	0.44	+2.82

without glycosuria. On the other hand, occasional partially depancreatized animals have been described in which the D:N ratio was that of "total diabetes" and yet the cachexia (increased protein metabolism) was absent. Allen[26] has been able by excessive feeding of partially depancreatized dogs to develop a condition which he considers a very satisfactory imitation of human diabetes; in these dogs there is no increase in the protein catabolism. Although he is one of the staunchest supporters of the parallelism between such dogs and human diabetics, and of the dictum that "without disease of the pancreas there is no diabetes," he believes that the azoturia in the totally depancreatized dogs was due to other factors than those which caused the disturbance in carbohydrate metabolism. That is, in his opinion, the pancreas possesses other internal secretions in addition to that controlling carbohydrate metabolism, and in human diabetes these other functions are not disturbed. Even the most ardent adherents to the

25. Falta, W.; Grote, F., and Staehelin, R.: Versuche über Stoffwechsel und Energieverbrauch an pancrealosen Hunden, Hofmeister's Beitrage **10**:199, 1907.

26. Allen, F. M.: Glycosuria and Diabetes, Cambridge, 1913, pp. 427, 505.

hypothesis of the pancreatic origin of diabetes would not contend that there is as complete destruction of the pancreas in the human diabetic as there is in the depancreatized dog. Such animals by being deprived of the external secretion of the pancreas can no longer properly digest food and must accordingly be in a state of starvation. It is obvious that evidence of increased protein metabolism obtained from the study of depancreatized dogs must not be considered proof of a similar increase in human diabetes.

Lusk and others have shown [27] that in dogs with phlorhizin glycosuria the nitrogen excretion may be four or five times that of normal dogs. Allen [28] states that this is due (1) to the fever caused by the subcutaneous injection and is not always present if the drug is given by mouth, and (2) to the secondary breakdown of protein to replace the urinary loss of sugar in fasting or insufficiently fed animals. Sugar in doses above a certain quantity is burned and spares protein in the

TABLE 20.—STUDIES OF THE METABOLISM OF A SPONTANEOUSLY DIABETIC DOG (MAIGNON)

Régime	Carbohydrate as Desired	Meat, 500 Gm.	Starvation	High Fat
Days	4	2	1	10
Daily weight loss, gm.	300	250	300	0
Urea, gm.	12.24	34.00	16.38	5.00
Sugar, urine, gm.	125.47	51.71	19.17	3.78
Acetone, gm.	0.602	1.248	0.122	0.670

phlorhizinized as in the normal animal. Important as is the information concerning many of the processes of metabolism obtained by the use of phlorhizin, it may be applied only in a limited way to the problems of diabetes. Phlorhizin glycosuria and diabetes mellitus are two fundamentally different conditions.[28] The normal sugar content of the blood of the phlorhizinized subject, his ability to burn glucose in excess of a given quantity determined by the dose of the drug and the causation of his glycosuria by local renal disturbances offer sharp contrasts to the hyperglycemia of diabetes mellitus, the invariable appearance in the patient's urine of excess of ingested carbohydrate and his glycocuria because of a disturbance of the carbohydrate metabolism.

The studies by Maignon [29] of a dog who became diabetic spontaneously offer some interesting contrasts to the observations made on animals rendered "diabetic" by either phlorhizin or pancreatectomy. In Table 20 are found a summary of his experiments.

27. Reilly, F. H.; Nolan, F. W., and Lusk, G.: Phlorhizin Diabetes in Dogs, Am. J. Physiol. **1**:395, 1898. Lusk, G.: Ueber Phlorhizin-Diabetes, Ztschr. f. Biol. **42**:31, 1901. Mandel, A. R., and Lusk, G.: Respiration Experiments in Phlorhizin Diabetes, Am. J. Physiol. **10**:47, 1903.

28. Allen: Loc. cit., p. 617.

29. Maignon, F.: Du Rôle des Graisses dans la Glycogenie, J. Physiol. et Pathol. Gen. **10**:866, 1908.

The experiments of Benedict and Joslin [30] on the rate of nitrogen excretion of diabetics without food receive frequent mention in connection with the nitrogenous metabolism of diabetics. Allen [31] refers to this work as evidence of increase of nitrogen destruction, and Foster [32] similarly quotes these authors. If the evidence actually does show an increased protein destruction in the diabetic, it demands very careful consideration; it matters not whether this increase be held to be a specific action of some factor of the morbid state upon protein, or as one of the compensatory measures for the carbohydrate deficit, such an increase if real must be reckoned with in the preparation of a low protein maintenance diet.

The urines of thirteen fasting diabetics were collected in the morning and the hourly rate of excretion of nitrogen per kilogram of body weight determined. The average of all determinations was 8.4 mg. nitrogen per kilogram of body weight per hour, with variations among the individual cases of from 4.2 to 12.1 mg., and among different experiments in the same cases of as much as 5.3 mg. (from 4.2 to 9.5). In a series of fourteen normal subjects the average excretion per kilogram of body weight per hour was 6.8 mg., with variations between 4.8 and 8.9. Five of thirteen of the diabetic patients excreted less than the average of the normals, and three of fourteen of the normals excreted more than the average of the diabetics. The fact remains, however, that the average of the diabetics was higher than the average of the normals, and four of the diabetics eliminated more nitrogen than the highest of the normals.

If these cases be studied in relation to their degrees of emaciation, it will be noted that, in general, the more poorly nourished have the highest rate of nitrogen excretion. In Table 21 the subjects are arranged in the order of their rates of nitrogen excretion; added are columns showing the average weight for the age and height of each case as found in the actuarial tables, the number of pounds above or below this and the percentage of digression from this average.

Cases X and W were clinically only moderately severe, M was light and the rest were severe. It will be noted that if the difference between the weight of the patient and the average normal weight may be taken as a rough measure of the degree of emaciation the better nourished patients excreted less nitrogen than the more lean patients. The average nitrogen excretion of the seven patients showing the least loss of weight was 6.6 mg. per hour (the controls averaged 6.8 mg.) while the average of the other 6 was 10.3. The proper explanation of

30. Benedict, F. C., and Joslin, E. P.: Metabolism in Severe Diabetes, Washington, 1912, p. 112.
31. Allen, F. M.: loc. cit., p. 419.
32. Foster, N. B.: Diabetes Mellitus, Philadelphia, 1915, p. 173.

these figures then seems to be that, whereas none of these fasting patients could supply fuel for energy from the store of body carbohydrate, some had a sufficient store of fat to serve the purpose and to render it unnecessary for them to burn protein for fuel. These determinations offer further evidence of the ability of fat to save protein in the diabetic. The results are what one would predict from the laws of normal metabolism; they give no evidence of abnormal protein metabolism in the diabetic.

Very occasionally a case of unusually severe diabetes is seen in which even the power of burning the glucose derived from small amounts of protein is lost, as is indicated by the D : N ration of 3.65 : 1 on a carbohydrate free diet.[33] Mandel and Lusk,[34] for example studied carefully the metabolism of such a case . The data they obtained concerning his nitrogen metabolism are presented in Table 22.

TABLE 21.—HOURLY RATE OF NITROGEN EXCRETION PER KILOGRAM IN DIABETES MELLITUS
(BENEDICT AND JOSLIN)

Case	Age	Sex	Average N per K per Hr., Mg.	Weight		Height		Average Normal Weight	Digression	
				K.	Lbs.	Cm.	In		Lbs.	%
N	14	M.	12.1	31.5	63	146	57	95	−32	−34
P	17	M.	11.9	39.5	87	173	66	140	−57	−41
R	47	M.	11.6	55.3	112	181	71	177	−65	−37
X	25	M.	9.8	63.2	139	170	67	160	−21	−13
I	24	M.	9.5	40.0	88	176	69	152	−76	−50
T	43	M.	8.9	51.2	113	180	71	179	−66	−37
H	38	F.	8.4	54.1	119	150	62	129	−10	−8
U	37	F.	7.9	39.5	87	160	63	130	−43	−33
O	16	F.	6.9	52.6	116	173	68	138	−22	−16
M	57	M.	6.4	81.7	180	172	68	162	+18	+11
Q	14	M.	6.2	51.4	113	168	66	95	+18	+19
S	57	M.	5.5	58.9	128	177	70	169	−41	−24
W	18	F.	4.2	58.9	130	161	73	118	+12	+10

The fact that this patient was not in nitrogenous equilibrium when his food contained 19 gm. nitrogen, and that he lost 14 gm. body nitrogen when he was fed boullion only with a nitrogen content of 7.7 gm. is frequently cited as evidence of increased protein metabolism in diabetes. Even after the fuel value of the food which was useless to the patient because of his inability to utilize carbohydrate is subtracted, his total caloric intake was sufficient to supply his metabolic needs. A moment's thought, however, will show that the increase in protein metabolism can be entirely explained by his total inability to burn carbohydrate, rather than any disturbance in the protein metabolism inherent in the disease. Not only is carbohydrate itself unavailable for energy, but as has been pointed out, the fat is also unavailable to

33. Geylin, H. R., and Du Bois, E. F.: A Case of Diabetes Mellitus of Maximum Severity, J. A. M. A. **66**:1532, 1916.

34. Mandel, A. R., and Lusk, G.: Stoffwechselbeobachtungen an einem Fall von Diabetes Mellitus, Deutsch. Arch. klin. Med. **81**:472, 1904.

spare protein because it requires some carbohydrate combustion to do this.

Mosenthal has recently studied in two series of cases the maintenance diet in diabetes mellitus as determined by the nitrogen equilibrium. In the first study [35] he fed diets in which fat and protein were about equal gram for gram containing ten to fifteen grams of carbohydrate. He started with diets low in calories and increased them until nitrogen balance was established, always feeding equal amounts of protein and fat. With such diets he found that it was possible to establish nitrogen balance on a caloric intake equal to that required by a normal person, and in some cases it could be established at an even lower level. To provide from 1,500 to 2,000 calories it is necessary on a protein-fat diet containing equal quantities of protein

TABLE 22.—STUDIES OF METABOLISM OF A VERY SEVERE DIABETIC (MANDEL AND LUSK)

Date	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Urine		Stool N, Gm.	Nitrogen		
					Glucose, Gm.	N, Gm.		In, Gm.	Out, Gm.	Balance, Gm.
19		Mixed diet			137	23.3	1.3	....	24.6	.....
21		Mixed diet			119	24.0	1.3	....	25.3	.....
23		Mixed diet			150	22.2	1.3	....	23.5	.....
25	117.5	170.7	84.8	2,580	148	20.9	1.3	18.8	22.2	—3.4
26	117.5	170.7	84.8	2,580	144	19.0	1.3	18.8	20.3	—1.5
27	117.5	170.7	134.8	2,768	179	18.5	1.3	18.8	19.8	—1.0
28	117.5	170.7	184.8	2,956	210	17.7	1.3	18.8	19.0	—0.2
29	117.5	170.7	184.8	2,956	217	17.8	1.3	18.8	19.1	—0.3
1	113.1	164.0	6.6	2,207	83	17.5	1.3	18.1	18.8	—0.7
2	168.1	222.4	5.5	2,789	88	22.2	1.3	26.9	24.5	+2.4
3	168.1	195.1	5.5	2,552	96	24.1	1.3	26.9	25.4	+1.6
4	191.1	192.1	5.5	2,645	106	27.7	1.3	30.6	29.0	+1.6
15	48.1	0	0	.....	85	21.7	...	7.7	21.7	—14.0

and fat to raise the protein ration to from 100 to 150 gm., and therefore Mosenthal found that nitrogen balance was established with relatively large amounts of protein—amounts that would not be tolerated without glycosuria by severe diabetics. Because of the fear of acidosis no effort was made to establish balance on low-protein, high-fat diets. Since he increased the protein content of the diet at the same rate as he did the fat it was to be expected that he would not feed enough calories to supply the body needs until the diet contained large amounts of protein. He showed, then, that when one feeds a diet containing equal weights of protein and fat, one is compelled to supply large quantities of protein in order to establish caloric equilibrium. He did not show that the diabetic requires more protein than the normal subject.

35. Mosenthal, H. O.: The Maintenance Diet in Diabetes Mellitus as Determined by the Nitrogen Equilibrium, Tr. Assn. Am. Phys. **32**:159, 1917.

In the second series of experiments,[2] an effort was made to determine the food value of alcohol, fat and protein by their abilities to spare nitrogen. After a few days on a control diet which usually contained about 70 gm. each of fat and protein and a small amount of carbohydrate, and which induced a negative nitrogen balance because of its low caloric content, he tried the effect of adding to the diets either alcohol or fat or protein or combinations of these. These additions brought the total calories up to from 1,500 to 2,000. Each such new diet was tried four to six days.

Only in occasional instances did the addition of fat establish nitrogen balance; since these were not severe diabetics, tolerating as they did from 150 to 200 gm. protein without glycosuria, the factors contributing to the enormous nitrogen output in such cases as that of Mandel and Lusk do not have to be considered. Mosenthal reached the conclusion that "the addition of an equal number of calories of protein, fat or alcohol to a low caloric, carbohydrate-free diet in cases of diabetes mellitus results in the assimilation of considerable amounts of nitrogen when protein is used, a favorable nitrogen balance in only occasional instances with fat, and no change in the nitrogen equilibrium when alcohol is given," and he stated that "this would point to a high protein diet as the most advisable low-caloric, carbohydrate-free diet by which to conserve the body tissues and furnish a maintenance ration for the diabetic."

We cannot accept these conclusions, however, because the experimental periods employed by Mosenthal were too brief to permit the subjects to totally rid themselves of the metabolic products of the previous diet or to readjust themselves to the new diet.

It was shown by C. Voit (Table 13) that it took fasting dogs five days to reach a common level of nitrogen excretion and that the higher the nitrogen content of the previous diet the more striking was the fall of nitrogen output from day to day. Weintraud showed (Table 17) in diabetics that the addition of fat to a high-protein, low-fat diet which induced a negative nitrogen balance would induce a positive balance only after several days had elapsed. A subject to whom he was feeding 111 gm. protein and 28 gm. fat had a negative balance of 6.7 gm. nitrogen. It was not until six days after the addition of 245 gm. fat to this diet that the first positive balance of only 1.34 gm. was attained. Three days later, on the same diet, the balance was 3 gm. We have had this same experience and have convinced ourselves that one is not justified in judging of the effect of a diet until it has been fed at least a week.

In two of Mosenthal's ten cases, the increase in fat followed immediately after a period of high protein feeding. The results are shown in Table 23.

In each of these cases the negative balance during a high-fat period following immediately after a high-protein period was greater than the negative balance during the control period when the total calories were a third less; this negative balance represented merely the continued excretion of the previously ingested protein. Case 5 had, in fact, been in nitrogen balance on the added fat on a previous occasion, when it did not follow a high protein period. The extract presented in Table 24 from the record of Case 7 in our series shows a similar lag in the excretion of nitrogen, with the subsequent sweeping-out during the following few days, and the eventual establishment of practical nitrogen balance.

During the period of high-protein feeding there was an apparent retention of nitrogen in the body, but during the succeeding low-protein

TABLE 23.—EFFECT OF PREVIOUS HIGH PROTEIN DIET ON NITROGEN BALANCE (MOSENTHAL)

Case	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	N Balance, Gm.	N Balance on Control Diet, Gm.
5	150.6	89.4	13.4	1,502	+2.6	−2.7
	71.2	125.6	12.1	1,506	−3.1	
8	150.2	89.4	13.5	1,503	+5.7	−1.5
	71.4	125.2	12.0	1,510	−3.4	

TABLE 24.—EFFECT OF PREVIOUS HIGH PROTEIN DIET ON NITROGEN BALANCE

	Food, Daily Average				Daily Average			Total for Period		
Days	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	N In, Gm.	N Out, Gm.	N Balance, Gm.	N In, Gm.	N Out, Gm.	N Balance, Gm.
5	185.0	99.1	14.6	1,700	29.58	18.38	+11.20	147.88	91.89	+55.95
6	32.7	145.9	26.0	1,560	5.23	14.75	−9.52	31.38	88.48	−57.10
6	33.5	150.1	25.4	1,585	5.26	5.41	−0.05	32.16	32.48	−0.32

period this nitrogen was all excreted; the total nitrogen ingested was 179.26 gm. and the total nitrogen excreted was 180.37 gm., practically a balance.

Another error in these short period experiments arises from the fact that the organism apparently requires some time to adjust itself to new dietetic conditions. Sherman believes that the variations between the results of numerous investigators of the minimum protein intake that would support nitrogen balance was due, in part, to "the differing lengths of the investigations and the extent to which the individual had accustomed himself to a low protein diet." He says further that "while it is conceivable that a small loss of body nitrogen may represent a real inadequacy of the intake, perhaps as regards some particular amino acids, yet it is usually much more probable that a small negative balance means simply that the body has not yet completed the adjust-

ment of its output to its intake and that a continuation of the experiment would have shown a smaller output."

Several of Mosenthal's patients were returned to the control diet immediately following the diet to which fat had been added; the control period, the fat period and the second control period are shown in Table 25.

In all these cases the saving of protein by fat showed in the period following the one during which the fat was given, as shown by the smaller negative nitrogen balance on the control diet after the fat feeding than before it. It seems safe to conclude that if the fat feeding had been continued a longer time in each case, nitrogen balance would have been established.

TABLE 25.—Delayed Effect of Addition of Fat in Establishing Nitrogen Balance

Case No.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories, Gm.	N Balance Gm.
1	71.4	70.5	12.3	999	−2.8
	71.3	125.1	12.1	1,506	−0.5
	71.7	70.6	12.4	1,001	−0.9
3	71.5	70.5	12.4	1,000	−3.0
	71.4	125.2	12.2	1,507	−2.9
	71.5	70.4	12.8	1,000	−1.3
6	71.4	70.5	12.4	1,000	−3.0
	71.4	125.2	12.2	1,507	−2.9
	71.5	70.4	12.8	1,000	−1.3
7	71.8	70.4	12.5	1,000	−2.9
	71.2	126.6	12.4	1,520	+1.2
	71.6	70.6	12.5	1,001	−0.9
	71.4	125.4	12.2	1,509	+1.7
	71.9	70.2	13.1	997	−1.5

As the result of these studies and others of a similar nature, the belief has become general that patients with diabetes mellitus require more protein for the establishment of nitrogen balance than do normal subjects, and that there is, as an inherent part of the disease, an abnormally high rate of protein metabolism with an increased elimination of nitrogen.

Most of the previous investigators have been handicapped by the fear of the use of fat in the treatment of diabetes mellitus, and have hence in none but the mildest cases, been able to increase the non-protein calories to a level that would satisfy the energy requirement without the production of glycosuria. The use of a high-fat, low-protein, low-carbohydrate diet in this clinic has enabled us to study in a more satisfactory manner than was hitherto possible, the minimal protein intake that will maintain nitrogen balance in the diabetic.

In Table 26 are presented the lowest diets on which nitrogen balance was established in our series. It must be remembered that this does not represent in every case the lowest possible level for balance, but the level at which, in the course of treatment, balance was established.

Some cases, as for example Case 6 in which the positive balance was at first over 2.5 gm. nitrogen or 16 gm. protein, could undoubtedly have been established in balance on a lower ration than that allowed.

In spite of the fact that these diets cannot be considered as the lowest on which nitrogen balance could have been established, they contained an average of 0.68 gm. protein per kilogram of body weight. This agrees with the figure found by Hindhede and others on normal subjects, and demonstrates that the diabetic patient may be maintained

TABLE 26.—Diets on which Nitrogen Balance was Established in Twelve Patients with Diabetes Mellitus

Case No.	Age, Years	Weight, Kg.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	N, Gm.	Protein per Kg., Gm.	Calories per Kg.	Per Cent. of Total Calories as Carbohydrate
1	56	63	34.3	168.4	6.9	1,680	5.49	0.54	27	1.6
2	68	66	39.2	231.4	13.8	2,295	6.27	0.59	35	2.3
3	37	60	54.1	240.0	13.4	2,430	8.66	0.90	41	2.2
4	18	42	28.5	162.8	9.9	1,615	4.49	0.68	38	2.4
5	21	50	37.8	165.6	8.2	1,650	6.05	0.75	33	1.9
6	49	70	65.0	197.0	9.9	2,065	10.04	0.93	30	1.9
7	22	59	32.5	150.1	25.4	1,585	5.26	0 53	27	6.4
8	36	69	55.5	207.8	38.7	2,245	8.80	0.79	33	6.9
9	63	30	31.8	157.4	23.8	1,640	5.09	0.63	33	5.8
10	80	90	51.4	239.1	33.9	2,265	8.22	0.57	25	6.0
11	22	55	40.6	200.2	25.0	2,065	6.50	0.74	37	4.8
12	18	42	30.0	179.6	14.7	1,795	4.80	0.71	43	3.3

in nitrogen balance on as low a protein ration as the normal subject. The average number of calories per kilogram of body weight given to this group of patients was 33.5 and of these calories, an average of only 3.8 per cent. were in the form of carbohydrate,

The average amounts of each of the foodstuffs used to make up these 33.5 calories are shown in Table 27. The fat in grams is ten times the carbohydrate in grams, or if the 58 per cent. of the carbohydrate that may be derived from protein be added, the weight of the

TABLE 27.—Average Amounts of Foodstuffs Per Kilogram of Body Weight Used in Establishing Nitrogen Balance

	Grams	Calories
Protein	0.68	2.72
Fat	3.28	29.51
Carbohydrate	0.32	1.27

fat is four and one half times that of the total carbohydrate. The carbohydrate calories are 3.8 per cent. of the total calories, or, if the protein carbohydrate be added, the total carbohydrate calories are only 8.6 per cent. of the total calories. Nitrogen balance can be established in the diabetic on diets low in protein whose energy is chiefly contained in fat.

To this law, however, there is an exception which for the sake of completeness must be mentioned again. A case such as that studied

by Mandel and Lusk, although very rare, is so severe as to have lost its ability to burn carbohydrate even in the small amounts necessary for the metabolism of fat. Such a diabetic who has so lost the ability to burn both carbohydrate and fat is inevitably thrown back on protein as a source of energy. The impossibility of satisfying his caloric requirement in other ways results in the excessive metabolism of protein. The rarity of such cases, however, makes them of little practical importance.

Several observations made during this study and already discussed should be mentioned again in this place. One case was cited which showed a delay in excretion of nitrogen during the administration of a high protein diet, with a sweeping-out during the following days of low protein feeding. As a result, there was an apparent large positive nitrogen balance during the high protein period, a large negative balance during the few days immediately following, and the ultimate establishment of balance after a few days (Table 23). Attention has also been called to the fact that nitrogen balance may be established on a given diet only after it has been administered for some time.

A diabetic patient suffering from advanced chronic pulmonary tuberculosis was studied. The data obtained were in accord with the observations of McCann and Barr and others regarding the increased protein destruction in tuberculosis.

CASE 13 (20-461).—Patient was a German-American ward tender, 28 years old, who was brought into the ward in impending coma after having tried to treat his diabetes with drugs and without diet. The diabetes was of about three years standing, and there had been no symptoms of tuberculosis. After a few weeks of treatment, he was in excellent condition as far as his diabetes was concerned, but his tuberculosis was advancing rapidly and came to a fatal termination about a month after the first nitrogen determinations were made. The diagnosis of tuberculosis was made by physical examination and confirmed by roentgenogram, acid-fast bacilli in the sputum and necropsy. The day to day data of the last month of this patient's life are presented in Table 28 and a summary in Table 29. He died September 25, without glycosuria or a positive ferric chloride test on his urine, and there was no evidence of acidosis as measured by the VanSlyke method. During the last six weeks his temperature, which had previously been normal, reached from 100 to 103 F. daily.

The contrast between this patient who showed so large a negative nitrogen balance on 0.8 gm. protein and 40 calories per kilogram of body weight, and the nontuberculous cases summarized in Table 25 is striking. The increasing nitrogen output in both urine and stool as death approached is also interesting.

An observation is made concerning the relation of nitrogen output to the caloric intake which is very important and which could be predicted from the fundamental laws governing protein metabolism established by the earlier workers in this field. As calories are added to

the diet in the form of fat the break-down of protein as measured by the nitrogen excretion is diminished. This ability of fat to save protein is especially evident on Cases 5 and 11 in which with unchanged protein intake the nitrogen elimination was markedly decreased by the addition of fat to the diet. It is equally striking that as the diet including protein is increased, with the chief increase, however, in fat, the nitrogen excretion falls. In Table 30 are presented data from six

TABLE 28.—PART OF RECORD OF CASE 13; DIABETES MELLITUS COMPLICATED BY CHRONIC PULMONARY TUBERCULOSIS

	Diet				Urine		Blood	Nitrogen					
Date	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Glucose, Gm.	Diacetic	Sugar, per Cent.	Urine, Gm.	Stool, Gm.	In, Gm.	Out, Gm.	Balance, Gm.	Wt., Lbs.
8/25	28.8	138.4	20.3	1,440	0	0	0.21	....	....	....	....	.....	93
26	29.7	141.3	21.8	1,480	0	0	....	....	....	....	....	.....	..
27	28.8	138.4	20.3	1,440	0	0	....	....	....	....	....	.....	..
28	30.9	112.6	16.6	1,205	0	0	....	....	....	....	....	.....	..
29	29.0	140.8	19.0	1,465	0	0	....	....	....	....	....	.....	..
Aver.	29.6	134.3	19.6	1,405	.	..	....	5.71	0.72	4.74	6.43	—1.69	
8/30 to 9/13	34.0	160.0	27.0	1,685	0	0	....	....	....	....	....	.....	90
9/14	34.9	179.7	27.3	1,865	0	0	....	....	....	....	....	.....	..
15	33.5	158.8	26.3	1,670	0	0	....	....	....	....	....	.....	91
16	33.0	142.2	28.6	1,540	0	0	....	....	....	....	....	.....	..
17	36.4	165.5	31.0	1,760	0	0	....	....	....	....	....	.....	..
Aver.	34.5	161.5	33.3	1,725	..	..	....	6.58	0.89	5.32	7.47	—1.95	
18	34.4	143.1	25.7	1,530	0	0	0.30	....	....	....	....	.....	94
19	34.7	182.6	24.4	1,880		0	...	....	....	....	....	.....	..
20	30.7	156.1	27.5	1,630	0	0	....	10.42	0.99	4.91	11.41	—6.50	..
21	34.7	151.1	26.4	1,605	0	0	....	7.45*	1.00*	5.55	8.45	—2.90	..
22	33.5	174.4	26.2	1,805	0	0	0.24	7.45*	1.00*	5.40	8.45	—3.05	94
23	35.0	209.5	26.7	2,130	0	0	....	6.26*	1.37*	5.00	7.63	—2.63	..
24	35.3	153.7	26.8	1,630	0	0	....	6.26*	1.37*	5.05	7.63	—1.98	..

* Average of two days' specimens.

TABLE 29.—SUMMARY OF CASE 13; DIABETES MELLITUS WITH PULMONARY TUBERCULOSIS

					Nitrogen				
Date	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Urine, Gm.	Stool, Gm.	In, Gm.	Out, Gm.	Balance, Gm.
8/25-8/29	29.6	134.3	19.6	1,405	5.71	0.72	4.74	6.43	—1.69
9/14-9/17	34.5	161.5	33.3	1,725	6.58	0.89	5.32	7.47	—1.95
9/20-9/24	33.8	169.0	26.3	1,760	7.57	1.15	5.41	8.72	—3.31
9/25	Death from pulmonary tuberculosis								

of the cases who show this decrease in protein metabolism; there are added to the tables the amounts of protein burned as estimated by multiplying the excreted nitrogen by 6.25 and the amount of glucose derived from this protein calculated as 58 per cent. of the protein. A diet too low in calories to meet the energy requirement may, because of its accompanying excessive nitrogen metabolism, produce (from the protein) large amounts of glucose which are avoided by the addition of more calories. In one of our cases the glucose so derived was

over 20 gm. To the diabetic this amount of glucose may be very important, and may be replaced by an equivalent amount of carbohydrates in the diet. By decreasing the ingested protein one may increase the carbohydrate in the diet without increasing the total carbohydrate metabolism. Furthermore, by decreasing the endogenous protein metabolism one may also increase the carbohydrate in the diet without increasing the total carbohydrate metabolism. Both of these desiderata may be achieved, with maintenance of nitrogenous equilibrium, through the addition of calories to the diet in the form of fat.

These facts show a fallacy of starvation in the treatment of diabetes. During the period of starvation, a subject well supplied with body fat burns this fat, and burns no less than he would if the fat were given him in the diet. This was demonstrated by Voit's experiment on a dog which has already been mentioned. In the case of the fasting lean diabetic, however, who cannot burn glucose, and whose supply of body fat is low, energy and heat are developed almost entirely by the combustion of protein. Destruction of body protein produces glucose exactly as much as does combustion of ingested protein. In the more severe grades of diabetes this is a factor of prime importance. Such patients become sugar free sooner if they are allowed a little carbohydrate and a relatively large amount of fat than they do if starved. One of our patients was starved ten days on several occasions before coming to us without his urine becoming sugar-free. On a diet containing about 15 gm. protein, 90 gm. fat and 15 gm. carbohydrate, he became sugar-free in ten days, and was in relatively excellent physical condition at the end of the period, in contrast to his exhaustion at the end of his periods of starvation. [A diabetic boy, 6 years old, failed to become sugar-free after seven days of starvation following a period of two weeks of a low caloric diet. On a diet containing 12 gm. protein, 85 gm. fat and 15 gm. carbohydrate his urinary sugar gradually decreased in amount and finally disappeared.] A young woman who had had a constant glycosuria during ten months on a diet containing 50 gm. protein, 20 gm. fat and 30 gm. carbohydrate and who had failed to become sugar-free on nine days of practical starvation became sugar-free in five days on a diet containing 15 gm. protein, 85 gm. fat and 14 gm. carbohydrate. The enormous metabolism of body protein during starvation with the production of large quantities of endogenous glucose explains, in part at least, the more favorable results of a diet relatively rich in fat.

The same undesirable production of glucose from body protein occurs to a lesser degree when an under nutrition diet is used in the treatment of diabetes mellitus. If the total calories fed the patient are not sufficient to supply caloric requirement, body protein is broken

down and glucose is produced. If an effort is made to supply enough protein in the diet to compensate for this excessive destruction of body protein, the ingested protein is a source of glucose. Just in so far as the carbohydrate burning function of the patient must be used for the combustion of glucose derived from protein, just so much more must his carbohydrate intake be limited. Fat offers the best agent in the diabetic for the sparing of protein, either endogenous or exogenous.

The increase in the metabolic rate, due to the specific dynamic action of protein, has been discussed.

That this increase in metabolism is not insignificant in such a condition as diabetes mellitus in which an effort is made to establish the metabolism at a low level is readily seen from a single example. Assuming that a fasting subject requires 2,000 calories a day, and

TABLE 30.—Decrease in N-Excretion with Increase in Caloric Intake

Case No.	Days	Calories	N In, Gm.	N Out, Gm.	Protein, Metabolism, Gm.	Glucose from Protein, Gm.
1	9	960	2.64	6.24	39.00	22.62
	6	980	2.61	6.87	42.94	24.91
	6	1,050	2.56	6.21	38.81	22.51
	5	1,500	5.42	5.72	35.75	20.73
	9	1,680	5.49	5.63	35.19	20.41
3	2	970	2.61	12.85	80.59	50.22
	4	1,400	4.77	11.81	73.81	42.81
	3	2,200	6.53	8.42	52.62	30.52
	5	2,420	8.06	8.12	50.75	29.43
4	8	1,410	3.98	7.65	47.81	27.73
	6	1,925	5.80	6.81	39.64	22.99
	8	1,925	5.80	5.77	36.06	20.91
5	5	475	2.46	9.34	58.38	33.86
	4	1,380	5.99	8.82	55.13	31.98
	3	1,380	5.99	8.10	50.63	29.37
	6	1,050	6.05	6.62	40.97	23.76
11	4	1,500	5.42	6.74	42.13	24.44
	4	2,205	8.22	5.00	31.25	18.12
12	2	1,530	4.96	6.96	43.50	25.23
	4	1,535	4.77	5.37	33.56	19.46
	4	1,795	4.80	4.86	30.37	17.61

that the heat eliminated as a result of the specific dynamic action of the foodstuffs is for protein, 30 per cent., fat 12 per cent. and carbohydrate 6 per cent., one may easily calculate the actual increase over the 2,000 calories that will result from various types of diets. A diet of the von Noorden type will contain 2,000 calories if they are divided as follows: protein, 200 gm.; fat, 120 gm.; carbohydrate, 30 gm. When the calories resulting from the specific dynamic action be added, however, the diet becomes the following: Protein, 286 gm.; fat, 136 gm.; carbohydrate, 32 gm.; calories, 2,496. The original calories are, on the other hand, contained in a diet which still contains but 30 gm. carbohydrate, but in which the protein and fat amount to 35 and 193 gm., respectively. The diet resulting from the addition of extra calories is as follows: Protein, 50 gm.; fat, 219 gm.; carbohydrate, 32 gm.; calories, 2,299. In the case of the high protein diet, the increase was

500 calories, or 25 per cent. of the fasting requirement, and in the case of the high fat diet, the increase was 300 calories, or 15 per cent.

In passing, attention should be called to the well known fact that nitrogen in the food in excess of the body requirement is excreted and is not stored. This is true in the diabetic as in the normal. In Case 6, for example, the patient was given 65 gm. protein in his food daily; during the first few days of this diet he had a positive nitrogen balance of more than 2.5 gm. daily, but after a few days the nitrogen excretion rose until he was established in practical balance. The high protein diet which was given Case 7 has already been discussed and it was pointed out that there was no real addition of nitrogen to the body. Furthermore, this patient was in balance at one time on 33 gm. protein a day and later on 55 gm. protein a day. Since the excess of nitrogen above the requirement is excreted there is no apparent advantage in feeding the diabetic patient large amounts of protein. On the contrary, as has been pointed out, this excess of protein is undesirable in the diet of the diabetic.

CONCLUSIONS

1. Nitrogen balance can be established in the diabetic according to the laws applicable to the normal subject provided his total caloric requirement can be satisfied. This implies that he can burn enough glucose to metabolize fat. Diabetics who cannot burn this small amount of glucose are extremely rare.

2. Protein metabolism above the minimal is undesirable in the diabetic because of (1) the great glycogenic property and (2) the large specific dynamic action of protein. Excessive protein metabolism results from a diet containing either too much protein or too few total calories.

MYCOTIC EMBOLIC ANEURYSMS OF PERIPHERAL ARTERIES *

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The pioneer investigators of the etiologic factors and pathologic processes in arteries have, in a large measure, centered their attention on the more imminent problems of the subject, so that today a wealth of information has been contributed to our knowledge of syphilis and sclerosis of vascular channels. Again, the results of more acute bacterial invasion on the wall of both the aorta and the peripheral arterial tree, as well as the various manifestations of the same organisms on the different arterial systems of the tree, have been studied carefully by others. This is especially true in the case of acute rheumatic fever, with or without an attending acute or subacute bacterial endocarditis, and, to a lesser extent, in other acute affections, notably scarlet fever, septicemia, typhoid fever and pneumonia. Thus our understanding of the modus operandi of acute bacterial invasion of the peripheral arteries has broadened. It is only natural that more accurate data on the latter manifestations of these infections have gone far to clarify our conception of the detailed materies morbi of such a condition as aneurysm. While the greatest stress has been placed on aneurysm of the aorta, particularly on aneurysms of syphilitic origin, nevertheless, a certain light has been thrown on the aneurysms as encountered in the arteries of a smaller caliber whether specific or nonspecific.

L. Koch,[1] in 1851, described a case of ruptured aneurysm of the superior mesenteric artery associated with a verrucose aortic endocarditis. Two years later, Tufnell [2] called attention to the co-existence of aortic endocarditis and popliteal aneurysm. In 1864, Chauffard [3] reported a similar aneurysm of the superior mesenteric artery while three years after Waterman [4] discussed one of the brachial artery in a case of valvular disease of the heart. While these cases suggested that the aneurysms were mycotic-embolic in origin, Ponfick,[5] in dis-

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2. Tufnell: Dublin Quart. J. M. Sc. **15**:371, 1853.
3. Chauffard: Union méd., 1865, p. 54.
4. Waterman: Western J. M., 1867, p. 584.
5. Ponfick: Virchows Arch. f. path. Anat. **58**: 1873.

cussing an aneurysm of the superior mesenteric artery in a patient with recurrent endocarditis, emphasized the mechanical effect rather than the infective character of the embolus. Legroux [6] recounted the instance of an infected embolus in the axillary artery, occurring in a girl with endocarditis. The embolus gave rise to an arteritis and resulted in aneurysm. Again, Jacobson [7] believed that his case of double aneurysm of the superior mesenteric artery precluded the possibility of an embolic origin. In this case there was a concomitant aortic endocarditis in which streptococci were isolated from the valvular vegetations. On the other hand, Humphry [8] described an instance of multiple embolic aneurysms of the pulmonary artery which had their genesis from vegetations around the orifice of the pulmonary artery. It was for Eppinger,[9] in 1887, however, to give the results of the first comprehensive study of a group of aneurysms of peripheral arteries which he called "mycotic-embolic." Since then analagous cases have been described by Lazarus,[10] Nasse,[11] von Gabriel,[12] Libman,[13] Schmey,[14] Routier,[15] Weinberger,[16] Roger and Gouget,[17] Lewis and Schrager,[18] Wieland,[19] Lindbom [20] and others. Save for the endeavors of the last three authors, few attempts have been made to collect the reported cases. At the present time it would appear that over a hundred well-authenticated instances of mycotic-embolic aneurysms of peripheral arteries are on record. Although no artery or system of arteries is exempt, this type of aneurysm apparently occurs most frequently in the superior mesenteric artery.

The term "mycotic-embolic" aneurysm, as coined by Eppinger,[19] implies that two factors are operative—the embolus and the mycosis or infection. It is imperative that this idea be borne in mind for it is recognized that an embolus which is not infective may produce an aneurysm, as in the case of a calcareous plaque cutting the intima (Libman [13]) and that all mycotic aneurysms are not necessarily embolic

6. Legroux: Semaine méd., 1884, p. 425.
7. Jacobson:: Bull. Soc. Anat., Par. **72**:569, 1897.
8. Humphry: J. Path. & Bacteriol. **17**:212, 1912.
9. Eppinger: Arch. f. klin. Chir. **35**:1, 1887.
10. Lazarus: Berl. klin. Wchnschr., 1891, p. 41.
11. Nasse: Deutsch. klin. Wchnschr. **24**:259, 1892.
12. Von Gabriel: Zentralbl. f. Chir. **31**:2, 1904.
13. Libman: Tr. New York Path. Soc. **88-91**, 1905.
14. Schmey: Cited by Roche and Burnaud: Semaine méd. **28**:145, 1908.
15. Routier: Semaine méd., 1905, p. 306.
16. Weinberger: Mitt. d. Gesselsch. f. inn. Med. u. Kinderh. **5**:4, 1906.
17. Roger and Gouget: Nouveau traité de medicine et de therapeutique de Bronardel et Gilbert, Paris **24**:25, 1907.
18. Lewis and Schrager: J. A. M. A. **53**:1808 (Nov. 27) 1909.
19. Wieland: Med. Cor.-Bl. d. Württemb. ärztl. Landesver. Stuttg. **82**:565, 1912.
20. Lindbom: Mitt. a. d. Grenzgeb. d. Med. u. Chir., Jena, Separatabdruck, 1914.

in nature, the infection being capable of entering the arterial wall by direct extension from the adventitia, by way of the vasa vasorum, as in the acute mycotic aneurysms of aorta (Osler,[21] McCrae,[22] Klotz [23]) or from the lumen at the point of contact of a septic embolus or thrombus. Not only have there been misconceptions and misunderstandings in the interpretation of these cases but also considerable controversy has arisen and opposite views have been offered to explain the sequence of events after the lodgment of the bacteria laden embolus. Consequently, we feel that a consideration of at least the possibilities of the order of pathologic events and an adaptation of the experiences and observations of other workers to the two such cases we have encountered at necropsy will not be amiss.

Fig. 1.—Case 1. Ventral surface of mesentery showing branches of superior mesenteric artery and hemorrhage into mesentery.

REPORT OF CASES

CASE 1.—A male, aged 38, was admitted to the hospital complaining of coughing, shortness of breath and intense pain in the epigastrium.

Previous Illness.—The history of his illness showed that he had had a number of attacks of "rheumatism" and that on more than one occasion there had

21. Osler: Allbutt's System of Medicine **6**:620, 1909.
22. McCrae: J. Path. & Bacteriol. **10**:373, 1905.
23. Klotz: J. Path. & Bacteriol. **18**:259, 1913.

been signs of a cardiac decompensation. The intense pain in the epigastrium, however, had been present only with the last attack.

Physical Examination.—The physical examination revealed an endocardial lesion of the aortic and the mitral valves associated with a moderate cardiac hypertrophy. The lesion was a regurgitant one at both orifices. The pulse was very rapid, between 120 and 140, weak and collapsing. The temperature was 102 F. There was some hypostatic congestion at the bases of the lungs. The abdomen was very painful to touch, and the abdominal muscles were quite rigid so that accurate palpation was difficult. The leukocyte count was 10,000.

Clinical Course.—The pain in the epigastrium, which commenced about twelve hours before his admission, persisted until his sudden death—a few hours after coming into the hospital. Although the pain gradually became less acute, at the onset it was very intense.

Necropsy.—At necropsy it was found that death had followed the rupture of an aneurysm of a branch of the superior mesenteric artery with a resultant hemoperitoneum. The heart showed hypertrophy and dilatation with a vegetative aortic, mitral and mural endocarditis, superimposed on a chronic sclerotic process of these valves. Passive congestion was present in the lungs and in the liver.

Description of Aneurysm.—The aneurysmal pouch was situated on the dorsal surface of the mesentery, near the attachment to the coils of the small intestine. It was irregularly oval in shape and measured 2.8 by 2.5 by 1.3 cm., being of such size as readily to accommodate a large marble. On the ventral surface, the aneurysm was supported by a massive blood clot while on the dorsum, where a ragged, linear slit indicated the site of rupture and the cause of the hemoperitoneum, it lay very close to the peritoneum. The aneurysm was continuous with a terminal branch of the superior mesenteric artery. The wall of the aneurysm was thin, though reinforced posteriorly by blood which had escaped into the mesentery, causing a marked thickening of it. The lining of the sac was roughly corrugated and consisted, for the most part, of a thick, friable layer of pinkish gray, granular organized blood clot. An intact rim of intima remained at the point where the artery entered the aneurysm. At a slightly higher level, another irregularly oval cavity, which could have easily admitted a hazelnut and represented a false aneurysm, occurred. It was encompassed by a thick layer of extravasated blood clot. The lining of the second cavity consisted only of several lamellae of well organized blood. Both cavities were connected by a small ragged opening. It was obvious that the true aneurysm had slowly ruptured at an earlier date with the formation of a false aneurysm and wholesale extravasation of blood into the mesentery. The process, as now seen, was relatively late so that the former embolus had disappeared in the thrombus. There was a stenosis of the artery at its entrance to the aneurysm. Above this, the arterial wall was thick and the intima was nodular.

Case 2.—The second aneurysm, that of the right posterior tibial artery, was recovered at necropsy from a man, aged 39, who for twenty-six weeks had pursued a typical clinical course of subacute bacterial endocarditis.

History.—He entered the hospital six weeks before his death, complaining of weakness with a little cardiac distress, particularly on moving in bed. At times he suffered from chilly sensations and felt feverish in the afternoon. This had been his condition since the onset of his illness, along with a progressive weakness. At this time the patient's temperature varied from 101 to 103 F., and the pulse from 120 to 130. There was a marked pallor.

Physical Examination.—The heart was somewhat enlarged and presented a double murmur which could be heard over the whole of the precordium, in the left axilla and at the back. The liver was palpable immediately below

the costal margin. Lying behind the head of the right fibula and just below it, there was an expansile round mass about the size of a small tangerine orange. One could palpate very easily a considerable portion of its surface. Its expansile pulsation was synchronous with the arterial pulse. This pulsating mass did not alter, to any great extent, the contour of the leg, although its pulsation was quite visible. The right leg below this appeared normal in every respect.

Laboratory Examination.—During the patient's stay in the hospital, which was a little over six weeks, *Streptococcus salivarius* was isolated from the blood stream on three occasions. The leukocyte count was about 12,000. Albumin, casts and red blood cells were present in the urine at various times.

Fig. 2.—Case 1. Dorsal surface of mesentery showing ruptured mycotic-embolic aneurysm of superior mesenteric artery.

Clinical Course.—Two weeks before his death he complained of a sharp lancinating pain in the region of the pulsating mass below the right knee. Almost immediately afterward a diffuse indurated swelling, which gradually extended to the lower portion of the calf of the leg, appeared. The leg became very painful, quite hard and of a dusky brown color. It was now impossible to outline, by palpation, the pulsating mass behind the head of the fibula, although one could still feel the pulsation here, as well as in the dorsalis pedis artery, and the foot appeared warm. In a few days, however, the foot became edematous and it was then impossible to palpate this artery. Even to the end there was no evidence that the circulation in the foot had been cut off. One week after this accident had occurred, signs of fluctuation

were present in the calf of the leg. It was considered wiser to refrain from an incision. The patient became more septic, dying about two weeks after the rupture of the aneurysm in the leg.

Necropsy.—At necropsy, the enlarged heart showed an acute and subacute vegetative mitral endocarditis, which had been planted on the thick, sclerosed valve cusps. Recent infarcts occurred in the spleen and kidneys.

Description of Aneurysm.—At the inferior margin of the right popliteus muscle, and lying posterior to the interosseous membrane, was an aneurysm which had evidently arisen from the tibial artery, a few centimeters distal to the bifurcation of the popliteal artery. The aneurysm was large, irregular in outline and presented three definite sacculations. Into the largest of these the artery opened from above. This compartment was the size of an English walnut, possessing a thin wall and a smooth, white, corrugated lining. With this main portion, two smaller sacs were associated. One, the size of a hazelnut, was tortuous and lined by a gray, laminated blood clot so that its wall was thick and stratified. The other sacculation, which was the smallest, lay posteriorly and inferiorly to the medium-sized one and its lining was identical with that of the main chamber. In the dependent tip of the smallest sac, a tiny opening was all that remained of the distal portion of the artery which had disappeared in the intense secondary cellulitis of the surrounding soft parts. Posteriorly and above, the main aneurysm had ruptured, as a result of which a laminated blood clot, the size of an orange, intervened between the exterior of the true aneurysmal sac and the soleus muscle. All the sacs contained dark red fluid blood, in addition to the thrombus which had obscured, no doubt, the original embolus. The popliteal artery was thick-walled and its intima was nodose. Where the posterior tibial artery entered the aneurysm, its thick, fibrosed wall was constricted, causing a narrowing of the lumen. It was clear in this case also, that a rupture of the true aneurysm with slow leakage into the contiguous soft parts had led to the formation of a false aneurysm. In addition, an extensive secondary suppurative cellulitis had wrought havoc with the leg from the knee to the foot. The popliteal vein showed no demonstrable change.

Microscopically, the sections of the walls of these two aneurysms presented an almost identical picture. The walls were made up chiefly of a relatively recent fibrous tissue. In the fibrous tissue, one was able to distinguish some smooth muscle, representing the remains of the muscular coat of the artery. Attached to the inner lining was a hyaline thrombus, well-infiltrated with polymorphonuclear leukocytes, lymphocytes, plasma cells and numerous endothelial cells containing blood pigment. This cellular infiltration extended through the wall to its periphery where there was considerable hemorrhage and marked invasion of all types of inflammatory cells. On staining for elastic tissue, remnants of the elastica interna were occasionally seen. In the deeper portions of the wall a few broken elastic fibrils were found. In the second case, gram positive cocci in short chains were noted in the cellular infiltration at the periphery of the wall. The aneurysmal wall, therefore, consisted largely of chronic inflammatory tissue. The finding of muscle and elastic tissue indicated that the media of the artery had shared in its formation.

Comment.—A comparison of the salient features of these two cases shows that in both an aneurysm of a peripheral artery occurred, one in the superior mesenteric and the other in the posterior tibial artery. Both were associated with a definite acute and subacute vegetatve endocarditis of the mitral or aortic valves. In one case infarcts were found in the spleen and kidneys. *Streptococcus salivarius* was isolated from the blood stream of one case during life. Unfortunately, the

sudden death of the other case prohibited antemortem cultures, while the autopsy cultures, taken 24 hours after death, showed only secondary invaders. No suggestion of syphilis was found in either case at necropsy. Both aneurysms had ruptured, at first slowly, with the formation of a false aneurysm. Clinically the rupture of the aneurysms was characterized by severe, sudden, lancinating pain, which persisted.

Fig. 3.—Case 2. Mycotic-embolic aneurysm of posterior tibial artery.

While no embolus was found at the aneurysmal sites in either case, it must be remembered that the aneurysms were far advanced and that well organized thrombi were present in them. This, in itself, could cause a complete disappearance of the original small embolus and does not preclude the liklihood of the one-time presence of the

embolus. From the evidence at hand, it seems clear that both aneurysms had their beginning in the bacteria-laden embolus which was swept off the affected heart valve, lodging at the bifurcation of the artery involved.

As had been stated, the aneurysms, as they came to us, represented the end results of an acute inflammatory process wherein, at this time, it was impossible to recognize the sequence of events from the primary endarteritis produced by the infected embolism. It has been definitely shown by Virchow [24] and Klotz [25] that a primary inflammation of the intima can occur and that the cellular exudate found in the intima appears to arise by a direct immigration of the wandering cells from the lumen of the artery. Eppinger,[9] in his exhaustive studies of mycotic-embolic aneurysms associated with acute vegetative endocarditis, held that the infected embolus produced an inflammation of the vessel wall at the point of contact. He believed that the infection spread from this point in the intima to the adventitia and that the aneurysm was due to the inflammatory process extending inwards from adventitia to the media, causing a rupture of the internal elastic lamina with subsequent arterial dilatation. Eppingers' work has been quite generally accepted, although other conceptions of the mode of formation of these aneurysms have been advanced. Benda [26] and, later, Wieland [19] considered the condition to be secondary to an extension of the inflammation in the intima through the elastica interna to the media and then to the adventitia, regarding the primary intimal lesion as an ulcerative endarteritis. In support of this view, McMeans [27] has shown that when the process is particularly acute and incited under conditions of septic thrombosis or infected embolus, there is destruction of the intima with extension of the inflammation through the vessel wall. On the other hand, where the process is not so acute, Klotz [28] has demonstrated that both the intima and the adventitia can be involved simultaneously and independently, the media escaping—stating that the infection reaches the intima from the lumen and the adventitia from the vasa or perivascular lymphatics. Furthermore, McMeans,[29] in studying the vascular changes in the meningeal arteries in septic meningitis, mentioned the primary polymorphonuclear infiltration of the intima with proliferation of the fixed cells of this coat and the extension of the process to the internal elastic membrane, with the later involvement of the media from both adventitia and intima. Moreover, inflam-

24. Virchow: Virchows Arch. f. path. Anat. **77**:380, 1879.
25. Klotz: Ref. McMeans, J. M. Research **32**:388, 1915.
26. Benda: Ergebn. d. allg. Path. u. Anat. **8**:236, 1902.
27. McMeans: J. M. Research **32**:388, 1915.
28. Klotz: Brit. M. J. **1**:1767, 1906.
29. McMeans: Am. J. M. Sc. **151**:249, 1916.

mation of both the intima and adventitia has been produced experimentally by Klotz [28] and others, employing *B. typhosus* and streptococcus in rabbits, by Saltykow [30] with *Staphylococcus aureus* and by Sumikawa [31] with turpentine and silver nitrate, where the inflammation occurred in all coats or in the intima alone. Benda [26] further believed that some of the aneurysms were metastatic in origin, the infection being carried to the wall through the vasa vasorum. Thus it would appear that the infection in a given case, as suggested by Chiari [32] in discussing tuberculosis of arteries, can and does occur either from within outwards or without inwards, whether carried by vasa or the perivascular lymphatics, as in periarterts nodosa (Klotz [33]) or by direct extension from without, as in the instance of secondary involvement from a neighboring tuberculous process—a view concurred in by Haythorn [34] in reporting such a condition. It is our belief that the ideas of both Eppinger and Benda are applicable to certain cases and, in addition, it is conceivable that the infection in the case of mycotic-embolic aneurysms may attack the artery from within outwards with direct extension from the intima through the elastica interna to the media and adventitia or, with the accompanying devitilization of the tissues at the point of lodgment of the embolus, any bacteria which may be present in the blood stream can enter the wall by way of the vasa and the mainstay of the arterial coat be approached, therefore, from both sides.

There are certain clinical phases of this subject which we would like, in conclusion, to emphasize. Mycotic-embolic aneurysms, though a very definite clinical entity, should be regarded only as an arterial manifestaton of the disease—"subacute bacterial endocarditis." This fact is important to remember, especially in reference to treatment. Some peripheral aneurysms, not of this type, can be treated radically by surgical measures but in these cases the local condition is not complicated by an endocardial infection. Radical surgical treatment of the mycotic-embolic aneurysm, as a rule, is a useless procedure because the cardiac condition remains unaltered. From the histories of cases of surgically treated peripheral aneurysms there is good reason to believe that a certain number were associated with an active endocardial lesion. The end result in these cases is practically always bad as the patient usually dies eventually from his endocarditis, if not from the immediate effects of the operaton. Finally we would call attention to the symptom of sharp stabbing pain at the time of rupture of the

30. Saltykow: Beitr. z. path. Anat. u. z. allg. Path. **43**:147, 1908.
31. Sumikawa: Beitr. z. path. Anat. u. z. allg. Path. **23**:242, 1903.
32. Chiari: Verhandl. Deutsch. Aerzte in Prag., Dec. 5, 1902.
33. Klotz: J. M. Research **37**:1, 1917.
34. Haythorn: J. A. M. A. **60**:1413 (May 10) 1913.

aneurysm. The pain is more severe and prolonged than that due to embolism which is a common occurrence in this form of endocarditis. Pain of this intense and persistent character in a case of subacute bacterial endocarditis may therefore be suggestive of a rupture of an aneurysmal sac. With the knowledge that infective embolism is of frequency in this disease, one wonders that mycotic-embolic aneurysms of peripheral arteries are not encountered more commonly. No doubt a certain number are overlooked so that it behooves the clinician and pathologist to be alert to the probabilities of this condition.

BOOK REVIEWS

NUTRITION AND CLINICAL DIETETICS. By HERBERT S. CARTER, M.A., M.D., Assistant Professor of Medicine, Columbia University. Second edition, thoroughly revised. Pp. 681. Philadelphia and New York: Lea & Febiger, 1921.

This volume affords an authoritative treatise on the highly important subject of nutrition and diet in health and disease. The book is divided into four parts. Part 1 deals practically entirely with food and nutrition in health. Part 2 deals with food, per se. Part 3 describes feeding in infants and children. Part 4 is devoted entirely to the subject of diet in disease.

The authors have brought the subject matter up to date and have added much new material in the chapters on chemistry, metabolism, and physiology of digestion, vitamins, etc. Much obsolete matter has been eliminated. In the last chapter of the book there are numerous tables which are accurate and very valuable for quick reference. The book is very readable and should be part of the armamentarium of most any medical practitioner.

LA GENESE DE L'ENERGIE PSYCHIQUE. J. DANYSZ. Librarie J. B. Bailliere & Fils, Paris.

M. Danysz, a scientist of renown in France, has, after devoting a large part of his life to material investigations in the Pasteur Institute, turned to less concrete and more speculative fields. Evolution has always attracted him, as seen in two volumes dedicated to the principles of evolution in infectious diseases and to the origin, evolution and treatment of noncontagious diseases. This has led him to fields purely metaphysical, and the present volume is a scientific and scholarly attempt to define the status of the human mind in relation to its surroundings—geological, biological, and sociological—past, present and future. Human intelligence, developing very slowly during the vast prehistoric ages, progresses with a constant acceleration, particularly in the recent, relatively short space of our authentic knowledge, and leaves us at our present point aghast at the possibilities, even certainties, of the future, with a mental power that will surpass physical forces. Present man is merely a momentary stage, will be rapidly surpassed, and man of the future will become, through this accelerated intellectual evolution, vastly superior—in fact, may dominate in the conquest of nature.

These seemingly startling predictions are no mere conclusions reached after hasty and enthusiastic considerations—but are deductions drawn from evidence presented by a large, sound and unusually complete summary of our existing state of knowledge. Inorganic chemistry, selective solubilities, chemical stability, followed by colloidal states of activity, are thoroughly considered before the biological realm is entered. Here the ordinary biological principles are discussed, followed by a minute consideration of the possibilities of evolutionary progression and the forces for and against such progress, including anaphylaxis, the rôle of vitamines, and the final result, the individual animal, later the various species of animals.

The final chapter is concerned with conclusions more of an ethical pedagogical, and psychological character—the differentiation and classification of individuals according to their reactions and the motives stimulating them, with an attempt to define the type most worthy of bearing the torch onward.

The volume is far above the level of the ancient metaphysicians, in spite of the rather startling conclusions. Fundamentally it is sound. There is no one point at which one can disagree or take exception—but though he has made a brave effort to bridge that seemingly limitless abyss between human anatomy

and physiology on the one side, and the cerebral processes on the other, M. Danysz has only led us a step nearer our own brink, from which we may, on arriving, possibly see across.

THE BLOOD SUPPLY OF THE HEART (IN ITS ANATOMICAL AND CLINICAL ASPECTS). By LOUIS GROSS, M.D., C.M., Douglas Fellow in Pathology, McGill University and Research Associate Royal Victoria Hospital, Montreal. With Introduction by HORST OERTEL, Strathcona Professor of Pathology, McGill University, Montreal. Pp. 165, 34 illustrations, New York, Paul B. Hoeber, 1921. Price, $5.00.

This monograph is a comprehensive work including a critical survey of the literature. The points of the author are well illustrated. The work is divided into eight chapters. In the first chapter the author discusses the various methods that have been employed in the study of the blood supply to the heart, and in conclusion describes his own technic, which is an improvement over any heretofore reported. In the second chapter the blood supply to the ventricles and auricles is described. The author points out that there is a wide variation in the distribution of the coronary arteries which he reserves for consideration in the third chapter. He overcomes this difficulty by describing the theoretical heart representing the average construction from the study of one hundred normal specimens. The fourth chapter details the result of a careful study of the blood supply to the neuromuscular tissue. The author concludes from the study of one hundred normal hearts that a specific blood supply exists for both the sino-auricular and auriculoventricular nodes, the main bundle, the first portion of the left limb and a large portion of the right limb of the neuromuscular system.

The fifth chapter deals with the blood supply to the heart valves. Six per cent. of the hearts studied showed valvular injection; of these the aortic cusp of the mitral valve was involved most frequently. The author believes that in those instances in which the valves were not injected, vessels did not exist. These conclusions were substantiated by microscopic examination of serial sections of the valves. He calls attention to the presence of musculature in the valves with blood vessels, and points out that the incidence of endocarditis is strikingly closely related to the existence of these two structures. He suggests that this may explain the frequency of right sided endocarditis in the fetus, left sided endocarditis in the child and the relative infrequency of this condition in adult life.

In the sixth chapter the anastomoses between the coronary arteries are discussed. The conclusions reached are largely confirmatory of those of former investigators. In the seventh chapter the venous supply of the heart is described. The eighth and final chapter deals with the changes in blood supply to the heart incident to different age periods. The author shows that in infancy and early childhood the vascularity is greatest on the right side. As the age advances the blood supply to the left side gradually becomes greater. Finally, in the sixth and seventh decades there is a great preponderance on the left side with a relative anemia of the right side. He attributes a part of the abundant vascularity of the left side to the development of the arteriae telea adiposae, or fat vessels. He considers this a compensatory mechanism in this critical period of life. He suggests that the insufficient blood supply to the right side may account for some of the sudden deaths in the aged and the high mortality from pneumonia at this period.

The most notable addition to the present conception of the blood supply of the heart is supplied by Chapters 4, 5 and 8. This work will be especially interesting and helpful to the anatomist and the physiologist in the investigation of fundamental problems concerning the heart. It will, perhaps, be equally interesting and valuable to the pathologist and clinician in a more comprehensive understanding of the pathologic processes and the clinical manifestation of cardiac disease.